Protocol

Protocol for: Jackson DJ, Wechsler ME, Jackson DJ, et al. Twice-yearly depemokimab in severe asthma with an eosinophilic phenotype. N Engl J Med. DOI: 10.1056/NEJMoa2406673

This trial protocol has been provided by the authors to give readers additional information about the work.

This supplement contains the following items:

1. Original protocol (206713), final protocol (206713), original protocol (213744), final protocol (213744), summary of changes (206713 and 213744)
2. Original statistical analysis plan (206713), final statistical analysis plan (206713), original statistical analysis plan (213744), final statistical analysis plan (213744), summary of changes (206713 and 213744)

TITLE PAGE

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Protocol Number: 206713

Compound Number or Name: GSK3511294

Brief Title: Placebo-controlled efficacy and safety study of GSK3511294 in participants with severe asthma with an eosinophilic phenotype

Study Phase: Phase 3A

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
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Manufacturer: GlaxoSmithKline

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SPONSOR SIGNATORY:

Jonathan Steinfeld Sr. Clinical Development Director	Date

Medical Monitor Name and Contact Information can be found in the Study Reference Manual (SRM).

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Brief Title: Placebo-controlled efficacy and safety study of GSK3511294 in participants with severe asthma with an eosinophilic phenotype

Rationale:

GSK3511294 is being developed as a long-acting (LA) subcutaneous (SC) injectable anti-interleukin-5 (anti-IL-5) therapy and is expected to deliver an efficacy and safety profile similar to current anti-IL-5 therapies with a reduced dosing frequency (once every 26 weeks). The aim of this study is to investigate the efficacy and safety, over a 52-week treatment period, of GSK3511294 100 mg SC given once every 26 weeks as adjunctive therapy in participants with uncontrolled severe asthma with an eosinophilic phenotype.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

Overall Design:

This study employs a multi-centre, randomised, placebo-controlled, double-blind, parallel group design to assess the efficacy and safety of GSK3511294 in participants with severe uncontrolled asthma with an eosinophilic phenotype despite standard of care (SoC) treatment with medium to high dose inhaled corticosteroid (ICS) plus at least one additional controller. All participants will receive study intervention as an adjunct therapy while remaining on their existing asthma therapy throughout the study.

Brief Summary:

The purpose of this study is to assess the efficacy and safety of GSK3511294 as an adjunctive therapy in participants with severe uncontrolled asthma with an eosinophilic phenotype. During the 52-week treatment period, participants will receive two doses (at Week 0 and Week 26) of add-on study intervention (GSK3511294 100 mg or matching placebo) by SC injection, while remaining on their existing maintenance asthma therapy (that excludes biologics) throughout the study. Assessments will include the annualised rate of clinically significant exacerbations and measures of lung function, asthma control, and safety.

Number of Participants:

Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125).

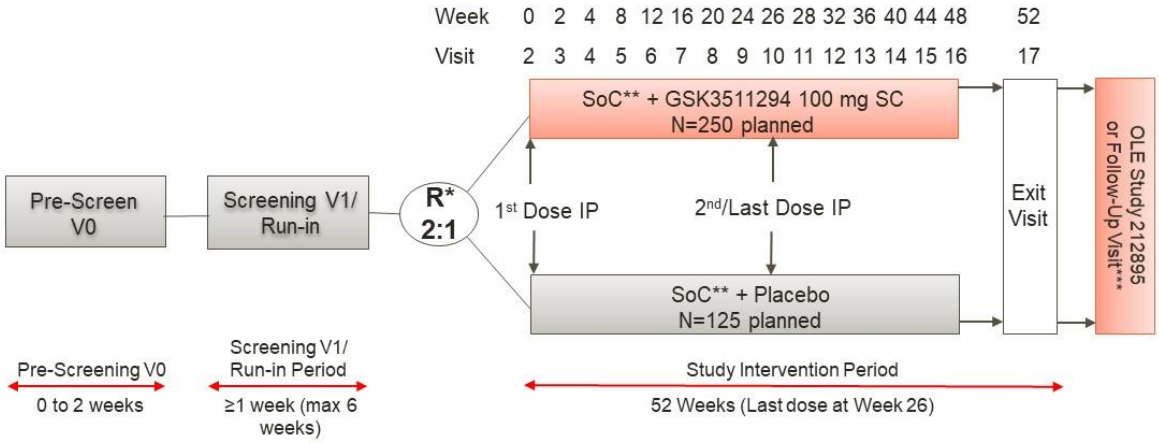
Intervention Groups and Duration:

The study will consist of a pre-screen period (0-2 weeks), a run-in period (1-6 weeks), and a study intervention period (52 weeks). After the run-in period, participants will be randomised in a 2:1 ratio using an interactive response technology (IRT) system in a blinded manner to receive either GSK3511294 100 mg or placebo by SC injection. Randomisation will be stratified based on baseline ICS dose (medium or high dose). Two doses of study intervention will be administered in the clinic: the first at randomisation Visit 2 (Week 0) and the second at Visit 10 (Week 26). Participants will be assessed at each scheduled visit (a total of 17 study visits) during the 52-week treatment phase. Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 10, Exit Visit 17, and WS Visit (if applicable).

Participants who receive both doses of study intervention and complete the Exit Visit will be eligible to participate in an open-label extension (OLE) study (Study 212895), during which they will receive two doses of open-label GSK3511294 100 mg SC over another 52 weeks. Participants who do not enter the OLE study will have a follow-up visit/call at Week 56.

Independent Data Monitoring Committee: Yes

1.2. Schema



** R = Randomisation: To be randomised participants without a historical blood eosinophil count of ≥300 cells/µL must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. Participants will remain on their standard of care (SoC) asthma therapy throughout the intervention period and will be randomised 2:1 to receive GSK3511294 (100 mg) or placebo.*

*** SoC = medium to high dose ICS (≥440 µg FP HFA daily or clinical comparability) plus additional controller. SoC asthma therapy to exclude biologics.*

**** OLE = Open label extension. Willing participants will continue directly into OLE Study 212895. Participants unwilling to continue will have a follow-up visit 4 weeks after the Exit Visit.*

1.3. Schedule of Activities (SoA)

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
General Eligibility Assessments																					
Informed consent [a]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote a.
Genetic sample informed consent [d]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote d.
Demography and childbearing status	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; All females must be assessed at Visit 1 to determine childbearing potential.
Inclusion/Exclusion criteria	X	X																			
Historical blood eosinophil count		X																			See footnote e.
Medical history		X																			Include cardiovascular (CV), CV risk factors, asthma, exacerbations, vasculitis, allergies and anaphylaxis.
Smoking status		X																			
Parasite screening		X																			Only required in regions with high-risk or for participants who have visited a high-risk region in the past 6 months. Use local laboratories for this test.
eDiary registration and training		X																			Conduct thorough eDiary training at Screening Visit 1 and throughout the study on as-needed basis.
Randomisation criteria			X																		Assess prior to randomisation; see footnote e.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
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Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Efficacy Assessments																					
Review for exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spirometry (pre- and post-bronchodilator FEV_1)		X	X								X							X	X		FEV_1=Forced expiratory volume in 1 second; Spirometry should not be conducted for participants with confirmed/suspected COVID-19 (see Section 8.2.3).
ACQ-5			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		ACQ-5=Asthma Control Questionnaire-5
Review eDiary (asthma symptoms, PEF summary)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PEF=Peak expiratory flow
HRQoL: PRO and Health Outcomes Assessments																					
SGRQ			X		X		X				X				X			X	X		SGRQ=St. George's Respiratory Questionnaire
PROMIS (fatigue items)			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PROMIS= Patient-reported outcomes measurement information system
SNOT-22			X								X							X	X		SNOT-22=Sino-nasal Outcomes Test-22 Questionnaire
Complete ADSD/ANSD		←========= daily =========→							X	X	X	X	X	X	X	X	X	X			ADSD/ANSD=Asthma Daily/Nightly Symptom Diary; To be completed daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.
Clinician-rated response to therapy							X				X				X			X	X		
Patient-rated response to therapy							X				X				X			X	X		

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
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Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
PGI-S		X	X				X		X		X				X			X	X		PGI-S: Patient Global Impression of Severity (of asthma)
PGI-C							X		X		X				X			X	X		PGI-C: Patient Global Impression of Change (from baseline of asthma severity)
Safety Assessments																					
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Ensure maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications are reviewed.
Physical Examination		X																X	X		Include height and weight for the complete physical exam at Screening Visit 1. Height can be omitted for subsequent visits.
Vital Signs		X	X			X			X		X	X			X		X	X	X		
12-lead ECG		X	X								X							X	X		
AE/SAE Assessment	X [g]	X [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE=Adverse events; SAE=Serious adverse events; see footnote g.
Laboratory Assessments																					
Haematology with differential [f]		X [e]	X	X	X	X	X		X		X	X	X		X		X	X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing; see footnotes e and f.
Total IgE			X																		
Clinical Chemistry		X	X		X	X	X		X		X	X			X			X	X		Include liver chemistry.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
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Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Pregnancy Test (WOCBP only)		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	Serum pregnancy test should be done at screening Visit 1 and Exit Visit; urine pregnancy tests should be done for all other assessments; WOCBP=Women of childbearing potential; See Section 8.3.5 for additional information.
Urinalysis		X	(X)								X							X	X		Conduct at Visit 2 if not completed at Visit 1. Note: dipstick, send for analysis if abnormality is identified by dipstick
Anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			X																		ANA=antinuclear antibodies; MPO=myeloperoxidase; PR3=proteinase 3. Collected baseline sample will be stored and may be tested if necessary (see Section 7.5).
Complement C3 and C4			X				X				X				X			X	X		
PK sample			X	X	X	X	X		X		X	X	X		X			X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing.
Immunogenicity sample			X	X	X	X	X				X	X	X	X	X			X	X		
Blood biomarker sample			X				X				X				X			X			Sample will be stored and may be analysed for exploratory biomarkers (see Section 8.7.3) **China only:** Blood samples for exploratory biomarkers will not be collected from participants in China.
Genetics sample			←========== The genetics sample can be collected at Visit 2 or any visit after ==========→																		See footnote d.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
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Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Study intervention																					
Administer study intervention			X								X										Study intervention will only be administered in the clinic. Any scheduled assessments or sample draws should be performed beforehand. Monitor participant for at least 2h after administration (see Section 6.5).
eCRF/worksheets/other																					
Dispense Rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Register Visit in the IRT system	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	IRT=interactive response technology
Provide worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				The worksheet is a medical problems and healthcare utilisation worksheet.
Review worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
eDiary close out																		X	X		
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		eCRF=electronic Case Report Form

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	

a. Informed Consent must be obtained prior to initiating any study assessments. Pre-screening Visit 0 can occur any time from 0 to 14 days before Screening Visit 1.

b. Randomisation Visit 2 is 1 week after Screening Visit 1 but can be extended to up to 6 weeks after Visit 1 if, for example, a participant has an exacerbation during the run-in period. Results from Screening Visit 1 procedures must be available for review of randomisation criteria.

c. If a participant withdraws from the study, then the Withdraw from Study (WS) Visit should be conducted 26 weeks after the last administered dose of study intervention, i.e., at Week 26 if the second dose of study intervention was not received, or at Week 52 if the second dose of study intervention was received. A follow-up visit/call should also be conducted 30 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing.

d. Informed Consent for optional genetics research must be obtained before collecting a sample. **China only:** Genetic Informed Consent will not be collected from participants in China. Genetic blood samples will not be collected from participants in China.

e. To be randomised, participants without a historical blood eosinophil count of ≥300 cells/µL in the 12 months prior to Screening Visit 1, must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1.

f. For haematology samples collected after Randomisation, the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will not be reported to site staff and Sponsor (to maintain the treatment blind). However, sites will be sent total white blood counts throughout the study. Samples should be taken prior to dosing at Week 0 and Week 26 visits.

g. SAEs must be collected from signing of Informed Consent if considered related to study procedures.

2. INTRODUCTION

2.1. Study Rationale

Anti-IL-5 therapies have an established efficacy and long-term safety profile and are a cornerstone of severe asthma management for patients with an eosinophilic phenotype [GINA, 2020]. Three antagonists of IL-5 (mepolizumab and reslizumab) or its receptor (IL-5R) (benralizumab) are approved for severe asthma with an eosinophilic phenotype, as an add-on treatment administered every 4 to 8 weeks.

GSK3511294 is being developed as a LA SC injectable anti-IL-5 therapy and is anticipated to deliver an efficacy and safety profile similar to current anti-IL-5 therapies with a reduced dosing frequency (once every 26 weeks). The aim of this study is to investigate the efficacy and safety, over a 52-week treatment period, of GSK3511294 100 mg SC given once every 26 weeks as adjunctive therapy to participants with uncontrolled severe asthma with an eosinophilic phenotype.

2.2. Background

Persistent eosinophil inflammation is a feature of more than 50% of patients with severe asthma [Chung, 2014]. Several monoclonal antibodies (mAbs) targeting eosinophil inflammation have received marketing authorisation for asthma with an eosinophilic phenotype, including 3 targeting either interleukin-5 (IL-5) or its receptor (IL-5R): mepolizumab (Nucala), reslizumab (Cinqair/Cinqaero), and benralizumab (Fasenra). All three, by utilising blood eosinophils as a biomarker to predict patients likely to respond to therapy, have been shown to reduce asthma exacerbations, and improve lung function and health-related quality of life (HRQoL), in patients with asthma with an eosinophilic phenotype [Haldar, 2009; Castro, 2011; Pavord, 2012; Bel, 2014; Ortega, 2014; Castro, 2015; Bleecker, 2016; FitzGerald, 2016; Chupp, 2017].

Evidence supporting the tolerability of targeting IL-5/5R is provided by long-term extension studies for mepolizumab [Lugogo, 2016; Khatri, 2019; Khurana, 2019], reslizumab [Murphy, 2017], and benralizumab [Busse, 2019] as well as efficacy data in real-world evidence settings for mepolizumab [Harrison, 2020; Bagnasco, 2019; Pertzov, 2019; Schleich, 2020]. Clinical trial data over more than 10 years combined with real-world evidence, have demonstrated that treatments targeting the IL-5 pathway are both highly effective and well-tolerated. Based on this established efficacy and safety, anti-IL-5/5R therapies are now a cornerstone of severe asthma management and are endorsed by international guidelines for appropriate patients that continue to exacerbate despite optimised care with Step 4 or Step 5 treatment (medium and high dose ICS) [GINA, 2020].

GSK3511294 is a humanised, affinity matured mAb that blocks human IL-5 binding to its receptor and belongs to the established class of anti-IL-5 therapies for severe asthma management. Compared with mepolizumab, GSK3511294 contains 7 amino acid substitutions to the heavy chain sequence: 4 amino acid changes introduced in the heavy chain variable region and 3 amino acid changes (YTE) in the Fc region. The resulting antibody has increased affinity and half-life. Evidence to date indicate that these amino

acid changes extend the pharmacokinetics (PK) and pharmacology of GSK3511294 to enable less frequent dosing with an anticipated similar efficacy and safety profile relative to mepolizumab (administered chronically).

Long-acting alternatives that can be administered on a less frequent basis are recognised as successful approaches for chronic indications. As a LA anti-IL-5 therapy, GSK3511294 is anticipated to have an efficacy and safety profile that is similar to those of the currently-approved therapies in its class, but with a single administration every 26 weeks, as opposed to the current regimen of every 4 weeks for mepolizumab and reslizumab, or every 8 weeks for benralizumab (every 4 weeks for the first 3 doses).

A detailed description of the chemistry, pharmacology, and safety of GSK3511294 is provided in the current Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2016N295843_03 or later].

2.3. Benefit: Risk Assessment

Summaries of findings from non-clinical studies conducted with GSK3511294 and completed FTIH study 205722 can be found in the current IB [GlaxoSmithKline Document Number 2016N295843_03 or later]. The following section outlines the risk assessment and mitigation strategy for this protocol:

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention GSK3511294		
• Allergic reactions including anaphylaxis.	• Allergic reactions with the most severe form being anaphylaxis (see Appendix 8), are potential risks associated with mAbs. • No allergic reactions or anaphylaxis have been reported with GSK3511294 in FTIH study 205722 in participants with mild to moderate asthma. One participant reported an event under Hypersensitivity SMQ with preferred term of rash verbatim "localised rash both bends of arms", 82 days post 30 mg SC dose of GSK3511294. The event was non-serious, of mild intensity, resolved within 10 days and was considered unrelated to the study intervention by the investigator.	• Daily monitoring of serious adverse events (SAEs) by Medical Monitor/SAE coordinator; regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GSK safety review team. • Use of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 8). • Participants will be monitored in clinic for immediate hypersensitivity and any other untoward effects for a minimum of 2 hours post-injection (both at randomisation and at Week 26). In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study intervention, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care if appropriate. • An independent data monitoring committee (IDMC) will review unblinded safety data at regular intervals.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Participants with severe allergic reaction/anaphylaxis with no alternative explanation after the first dose will not receive another dose.
• Type III Hypersensitivity (Immune complex disease/vasculitis)	• Adverse effects of vascular inflammation consistent with immune complex disease were observed in 1 female monkey in the 1-month toxicity study after administration of 10 mg/kg. A further monkey had a minimal focal inflammation after administration of 100 mg/kg. Immune complex disease was not observed in the 6-month repeat dose (2 doses) study at the same doses. It is unknown if this will translate to humans as preclinical models are not necessarily predictive of clinical findings in humans. • No AEs of Type III hypersensitivity have been reported with GSK3511294 in FTIH study 205722 in participants with mild to moderate asthma (36 participants received GSK3511294; 12 participants received placebo).	• Participants with current diagnosis of vasculitis will be excluded. Participants with high clinical suspicion of vasculitis at screening will be evaluated and excluded from enrolment if diagnosed (Section 5.2). • Daily monitoring of SAEs will be done by Medical Monitor/SAE coordinator; regular systematic review of adverse event (AE)/SAE data from ongoing studies will be performed by a GSK safety review team. • IDMC will review unblinded safety data at regular intervals; any events suggestive of immune complex disease will be reviewed by a rheumatologist (member of the IDMC). • Protocol guidance on early identification of vasculitis events is provided (see Section 7.5). • Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation after the first dose will not receive another dose of study intervention (see Section 7.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• Immunogenicity, anti-drug antibodies (ADAs)	• Biopharmaceutical products may elicit ADAs and neutralising antibodies (NAb), which have the potential to modulate PK or pharmacodynamics (PD), or to produce adverse reactions. • In FTIH study 205722, none of the participants tested positive for ADA at baseline. Overall, 9 participants (25%) had confirmed positive results for ADA at any time post-baseline, primarily in the GSK3511294 30 mg dose group (5 participants), which was also the group with the highest total serum IL-5 concentrations. This apparent correlation warrants further investigation. There were no major differences observed in the GSK3511294 plasma concentration-time and blood eosinophil count-time profiles as well as AE reporting between ADA-positive and ADA-negative participants. Neutralising antibodies were not tested in this study.	• Blood samples will be collected for detection of both ADA and NAb (see Section 8.8).
• Local injection site reactions	• A potential risk of any drug delivered via injection. • No injection site reactions were noted in the preclinical studies. • In the GSK3511294 FTIH study 205722, injection site reactions were reported by one (3%) participant who received	• Daily monitoring of SAEs by Medical Monitor/SAE coordinator; regular systematic review of AE/SAE data from ongoing studies by GSK study team and/or GSK safety review team. • The IDMC will review unblinded safety data at regular intervals.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	GSK3511294 and one (8%) participant who received placebo.	
• QTc prolongation	• Four monkeys in the 6-month repeat dose monkey study administered 100 mg/kg every 3 months (2 doses) were observed to have QTc prolongation (mean change of 18 msec relative to vehicle control value) during Week 14. • In the GSK3511294 FTIH study (205722), a total of 2 participants had an elevated post-baseline QT interval corrected using Fridericia's formula (QTcF) value of potential clinical importance based on average from triplicate assessment: one on GSK3511294 100 mg SC (Week 2: 467 msec [all subsequent assessments were <450 msec and Day 1 pre-dose was 450 msec]) and one on placebo (Week 36: 455 msec [last assessment on study and Day 1 pre-dose was 414 msec]).	• ECGs will be performed according to timepoints specified in the SoA (Section 1.3) and the assessment will be done as specified in Section 8.3.3. • Participants with QTc prolongation on screening will be excluded (criterion 15, Section 5.2). • Participants with a pre-existing clinically significant cardiac medical condition are excluded (criterion 7, Section 5.2). • Participants who meet QT stopping criteria as specified in Section 7.1.2 will not receive another dose of study intervention. • The IDMC will review unblinded safety data at regular intervals.
• Risk of GSK3511294 affecting an unborn baby.	• Reproductive studies have not been conducted with GSK3511294; however, in the 6-month repeat dose monkey study no changes were observed in reproductive organs. Seminiferous tubules were evaluated with respect to their stage in the spermatogenic cycle and the integrity of the various cell types present within the different stages in sexually mature males.	• Participants who are pregnant, breastfeeding, or plan to become pregnant at Screening are excluded (criterion 19, Section 5.2). Participants who become pregnant during the study will not receive another dose of study intervention (see Section 7.1). • All female participants will be assessed at screening to determine childbearing status. Female participants of childbearing

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	No cell or stage specific abnormalities were noted. • In addition, there is a low reproductive risk associated with the IL-5 target mechanism (as shown in pre-clinical reproductive toxicology studies of mepolizumab and reslizumab), a low genotoxic concern for mAbs in general, and a low transfer of mAbs into semen due to the inability of large molecular weight proteins such as GSK3511294 to access pivotal cells in the testes [Setchell, 1975; Pollanen, 1995; Pollanen, 1989; Setchell, 2001; Sohn, 2016], the risk of adverse effects on spermatogenesis is considered minimal. Therefore, male participants are not required to use contraception.	potential must be using a highly effective contraceptive method from at least 14 days prior to first dose and until 30 weeks after the last administered dose as described in Section 10.4.2.
Study Procedures		
• Potential risk for injury with phlebotomy.	• Risks with phlebotomy include bruising, bleeding, infection, nerve damage.	• Procedures to be performed by trained personnel (i.e., study nurse).

2.3.2. Benefit Assessment

Current clinical data from approved anti-IL-5/5R mAbs (mepolizumab, reslizumab, and benralizumab) demonstrate clinical utility in the treatment of conditions associated with elevated eosinophil levels, such as severe asthma with an eosinophilic phenotype. Mepolizumab 100 mg SC (every 4 weeks) is approved as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype. The safety profile of mepolizumab is favourable.

As a LA anti-IL-5 mAb, GSK3511294 is anticipated to provide the same clinical benefit with a similar safety profile compared with mepolizumab and others in its class and with the added benefit of an extended duration of action requiring less frequent SC dosing (once every 6 months). As such, GSK3511294 may offer the convenience of an improved dosing schedule.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures being implemented to minimise risk to participants in this study, the potential risks of participating in this study are justified by the anticipated benefits that may be afforded to participants with severe uncontrolled asthma with an eosinophilic phenotype; therefore, the Sponsor considers that the investigation of the efficacy, and safety of GSK3511294 is justified in this study with a positive benefit: risk ratio.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks
Other	
• To investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	• Time to first clinically significant exacerbation[a] • Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit • Change from baseline in SGRQ total score at discrete timepoints during the 52-week period • Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period • SGRQ total score responder status at Week 52 (responder defined as achieving ≥4-point reduction from baseline) • ACQ-5 score responder status at Week 52 (responder defined as achieving ≥0.5-point reduction from baseline) • Change from baseline in Patient-Reported Outcomes Measurement Information Systems (PROMIS) Fatigue items score at

Objectives	Endpoints
	discrete timepoints during the 52-week period • Change from baseline in Asthma Daily Symptom Diary (ADSD)/ Asthma Nightly Symptom Diary (ANSD) weekly mean score at specified timepoints during the 52-week period • Change from baseline in awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean • Change from baseline in morning peak expiratory flow (PEF) 2-week mean • Change from baseline in daily asthma symptom scores 2-week mean • Change from baseline in mean number of occasions of rescue medication use/day 2-week mean • Mean number of days with oral corticosteroids (OCS) usage over 52 weeks • Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period • Change from baseline in Sino-nasal Outcomes Test-22 (SNOT-22) score at discrete timepoints during the 52-week period
• To investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient- and clinician-rated response to therapy • patient global impression of asthma severity and its change from baseline	• Patient-rated response to therapy at discrete timepoints during the 52-week period • Clinician-rated response to therapy at discrete timepoints during the 52-week period • Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period • Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during the 52-week period
• To investigate the PD effects of GSK3511294	• Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period

Objectives	Endpoints
• To investigate the PK of GSK3511294	• GSK3511294 plasma concentration at discrete timepoints during the 52-week period
Safety	
• To evaluate the safety and tolerability of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Incidence of AEs/SAEs • Laboratory parameters, including haematological and clinical chemistry parameters • Vital signs including blood pressure (BP), body temperature, and pulse rate • ECG assessments • Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294
Health Resource Use	
• To further evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on healthcare utilisation on top of existing asthma therapy	• Healthcare utilisation for asthma including hospitalisation, ED, and physician office/clinic visits

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

3.1. Primary Estimand

Population: Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Treatment comparison: GSK3511294 + SoC compared with placebo + SoC

Endpoint: Annualised rate of clinically significant exacerbations over 52 weeks

Main intercurrent events anticipated:

- Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e. regardless of the intercurrent event occurring
- Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be handled with a hypothetical strategy i.e. had the intercurrent event not occurred
- Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): to be handled with a treatment policy i.e. regardless of the intercurrent event occurring

Summary measure: Ratio of the rates of clinically significant exacerbations between GSK3511294 + SoC and placebo + SoC

For further details, see Section 9.4.

3.2. Secondary Estimands

Population: Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Treatment comparison: GSK3511294 + SoC compared with placebo + SoC

Endpoints:

- Change from baseline in SGRQ at Week 52
- Change from baseline in ACQ-5 at Week 52
- Change from baseline in pre-bronchodilator FEV_1 at Week 52
- Annualised rate of clinically significant exacerbations requiring hospitalisation and/or ED visit over 52 weeks

Main intercurrent events anticipated:

- Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e. regardless of the intercurrent event occurring
- Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be handled with a hypothetical strategy i.e. had the intercurrent event not occurred
- Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): to be handled with a treatment policy i.e. regardless of the intercurrent event occurring

Summary measures:

- Difference in mean change from baseline in SGRQ at Week 52
- Difference in mean change from baseline in ACQ-5 at Week 52
- Difference in mean change from baseline in pre-bronchodilator FEV_1 at Week 52
- Ratio of the rates of clinically significant exacerbations requiring hospitalisation and/or ED visit

between GSK3511294 + SoC and placebo + SoC.

For further details, see Section 9.4.

4. STUDY DESIGN

4.1. Overall Design

This study employs a multi-centre, randomised, placebo-controlled, double-blind, parallel group design. The study will recruit adults and adolescents (≥12 years) with a confirmed diagnosis of severe asthma with an eosinophilic phenotype and who are on a regimen of medium to high dose ICS (≥440 mcg fluticasone propionate [FP] hydrofluoroalkane product [HFA] daily, or clinically comparable [GINA, 2020; see Appendix 10]) plus at least one additional controller medication, with evidence of bronchodilator reversibility or airway hyperresponsiveness as measured by methacholine/histamine challenge. Eligible participants must have uncontrolled asthma with a history of repeat exacerbations (≥2 exacerbations in the previous 12 months) while on their existing maintenance asthma therapy that excludes any biologics. Participants will be required to have a blood eosinophil count of ≥150 cells/µL at screening or ≥300 cells/µL documented in the 12 months prior to screening. Participants who have received any anti-IL-5/5R mAb therapy within the last 12 months will be excluded from this study.

Participants will attend a Pre-screen Visit (Visit 0) to sign consent and a Screening Visit (Visit 1; may be done on the same day as Visit 0) for eligibility assessments (see Section 8.1). At the conclusion of the run-in period (Visit 2), participants who meet the pre-defined criteria (see Section 5.1 and Section 5.3) will be randomised in a 2:1 ratio to receive either GSK3511294 100 mg or placebo, administered SC (at Week 0 and Week 26) in the clinic via a pre-filled safety syringe (PFS) as an adjunct therapy. Randomisation will be stratified based on baseline ICS dose (medium [approximately 25% of participants] or high [approximately 75% of participants]; see Appendix 10). Participants will remain on their existing stable maintenance asthma therapy throughout the study (See Section 6.9 for details on concomitant medications). See Section 4.1.1 for additional details on the study phases, duration, and treatment arms.

The primary outcome measure will be the annualised rate of clinically significant exacerbations (i.e. exacerbations requiring systemic CSs and/or hospitalisation and/or ED visit [see Section 8.2.2]) measured over the 52-week treatment period. Additional efficacy assessments will include lung function (pre- and post-bronchodilator FEV_1), asthma control (ACQ-5), HRQoL measured with SGRQ, fatigue (PROMIS items), nasal symptoms (SNOT-22 questionnaire), daytime and night-time asthma symptoms (ADSD/ANSD), and daily electronic diary (eDiary) parameters including peak flow, rescue use, daily symptoms and nocturnal awakening due to asthma (see Section 8.2).

The study will include safety (see Section 8.3 and Section 8.4) and immunogenicity (see Section 8.8) assessments to characterise the safety profile of GSK3511294 100 mg SC following repeat dosing. In addition, blood samples will be collected for assessment of PD effects (blood eosinophils) (see Section 8.7) and PK of GSK3511294 (see Section 8.5).

After randomisation, all participants will be encouraged to remain in the study and complete all scheduled visits, regardless of whether they receive the second dose of study intervention at Week 26. Participants who experience any of the study intervention

discontinuation conditions (listed in Section 7.1) will not receive another dose of study intervention.

Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 10, Exit Visit 17, and WS Visit (if applicable). Participants who are unable to attend their scheduled clinic visits due to COVID-19 restrictions or other unexpected events may complete some visits at home (see Appendix 11). Note: study intervention will only be administered in the clinic (at Week 0 and Week 26 visits).

4.1.1. Study Phases, Duration and Treatment Arms

At pre-screening, participants will be requested to participate in the study for a maximum of 60 weeks (Visit 0 to the Exit Visit, inclusive) or 64 weeks if not continuing into the OLE Study 212895 (Visit 0 to the Follow-up Visit, inclusive).

During the study, participants will remain on their existing maintenance asthma therapy whilst completing all phases of the study described in Table 1.

Table 1 Study Phases

Phase	Phase Title	Duration	Description
1	Pre-screening (Visit 0)	0-2 weeks	Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) but must be completed prior to initiating any Visit 1 procedures
2	Screening (Visit 1) and Run-in	1-6 weeks	Participants who meet all the eligibility criteria at Screening (Visit 1) will enter the run-in period for a minimum of 1 week and a maximum of 6 weeks. The run-in is intended to assess the participant's compliance with study-related procedures and continued eligibility for the study as well as to collect baseline eDiary data. Participants who experience an asthma exacerbation during the run-in period should receive treatment for their exacerbation and remain in the run-in period until the investigator considers that the participant has returned to their baseline asthma status for at least one week. The participants that are not eligible to continue in the study at the end of the run-in period will be deemed run-in failures, but may be rescreened after consultation with the Medical Monitor (Section 5.5).

Phase	Phase Title	Duration	Description
3	Study Intervention (Visit 2-Visit 17)	52 weeks	Participants who meet the randomisation criteria will enter the 52-week treatment period and will be randomised to receive either add-on **GSK3511294 (100 mg) or matching placebo in a 2:1 ratio.** During the treatment phase, a total of 2 doses of study medication will be administered SC via PFS: at Week 0 (Visit 2) and Week 26 (Visit 10).[a] Clinic visits will occur at Week 0, Week 2, Week 4 and every 4 weeks thereafter with an additional clinic visit at Week 26 for the administration of the second dose of study intervention. The study intervention period will conclude with the Exit Visit at Week 52 (Visit 17).
Only participants who choose not to enter the OLE study will complete the phase below:			
4	Follow-up	4 weeks	Participants will complete a Follow-up visit/call 4 weeks after the Exit Visit; this visit/call will capture AE/SAE assessments and a urine pregnancy test result. At the end of the Follow-up visit/call, participants will be prescribed appropriate alternative asthma therapy at the physician's discretion, if required.

a. Participants who experience any of the study intervention discontinuation conditions listed in Section 7.1 will not receive another dose of study intervention but will be encouraged to remain in the study and complete their remaining scheduled visits/assessments.

4.1.2. Treatment after the End of Study

Participants who receive both doses of double-blind treatment and complete the Week 52 Exit Visit will be eligible to participate in the OLE study 212895. See Section 6.7 for details.

Participants who are not entering the OLE study 212895 will enter a 4-week follow-up period and complete the study with a Follow-up visit/call at Week 56. After study completion, appropriate alternative asthma therapy may be prescribed at the physician's discretion.

4.1.3. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilised in this study to ensure external objective review of the data in order to protect the ethical and safety interests of participants and to protect the scientific validity of the study (see Section 10.1.5).

4.2. Scientific Rationale for Study Design

Population: This study is designed to evaluate the efficacy and safety of GSK3511294 100 mg SC as an adjunct therapy in participants with severe uncontrolled asthma with an eosinophilic phenotype. Participants should have uncontrolled asthma, as evidenced by repeat exacerbations, despite treatment with optimised background therapy consisting of maintenance ICS treatment and at least one additional controller. Participants are also required to have the requisite elevated blood eosinophil count (see randomisation criterion 1, Section 5.3) that is indicative of asthma with an eosinophilic phenotype. This population has been shown to benefit from add-on anti-IL-5 therapies such as mepolizumab [Pavord, 2012, Ortega, 2014; Chupp, 2017] and is therefore anticipated to benefit from GSK3511294.

Blood eosinophil count screening: A Screening blood eosinophil count threshold of ≥150 cells/µL at Screening Visit 1 or ≥300 cells/µL in the previous 12 months has been selected as a criterion to identify participants likely to respond to treatment with anti-IL-5 therapy, consistent with findings from previous trials with mepolizumab.

Primary efficacy endpoint: A primary efficacy endpoint of annualised rate of clinically significant exacerbations has been selected as a robust and clinically relevant measure of the direct benefit of GSK3511294 to a population with severe uncontrolled asthma with an eosinophilic phenotype. In the current study, the definition of clinically significant exacerbations (see Section 8.2.2), i.e. exacerbations treated with systemic CSs (intramuscular [IM], intravenous [IV], or oral) for 3 or more days and/or hospitalisation and/or ED visit, is consistent with previous trials with mepolizumab [Pavord, 2012; Ortega, 2014] and reslizumab [Castro, 2015].

Placebo-control design: An established randomised, double-blind and parallel-group study design will allow for a robust determination of participant response to GSK3511294 as an adjunct therapy to their maintenance asthma therapy. As such, the comparator arm in this study will be placebo plus continued maintenance asthma treatment. A 2:1 randomisation will be used in order to limit the number of participants randomised to placebo treatment and to provide more safety information on GSK3511294. All participants will continue to receive their optimised and stable maintenance asthma therapy throughout the entire duration of the study regardless of intervention arm assignment. The stable maintenance asthma therapy (per the inclusion criteria) will consist of medium to high dose ICS (≥440 mcg FP HFA daily, or clinically comparable [GINA, 2020; see Appendix 10]) with at least one additional controller medication e.g., long-acting beta-2-agonist (LABA), with or without maintenance oral corticosteroids (OCS). Participants who are treated with medium dose ICS will also need to be treated with LABA to qualify for inclusion.

Study Duration: A 52-week treatment period should allow sufficient time to assess whether GSK3511294 100 mg SC, administered as two repeat doses 26 weeks apart (at Week 0 [randomisation] and at Week 26), can reduce the annualised rate of clinically significant exacerbations to a similar extent to that observed with other anti-IL-5 mAbs. The study will also provide 12-month safety data with repeat dosing.

Run-in Period: The one-week (maximum 6 weeks) Run-in period allows for the assessment of participant understanding and compliance with the daily eDiary, to establish Baseline symptoms, and to allow adequate time for receipt of results from assessments collected at Screening Visit 1.

Open-label extension study: Following study completion, all eligible participants will have the option to participate in the OLE study to provide additional safety data (see Section 6.7).

Data collection after discontinuation from study intervention: The protocol objective is to collect data over the full study period, whether participants continue on study intervention or in the case of premature discontinuation from study intervention. However, the decision to continue in the study after premature discontinuation from study intervention remains the prerogative of the participant. Participants who agree to continue in the study after premature discontinuation from study intervention (for any reason) will continue to be contacted by the study site, either through in clinic visits or by phone as agreed with the participant, on a monthly basis (aligned to their study schedule) until the end of their planned 52-week participation and follow up contact 4 weeks later, to enable capture of post-intervention information.

4.2.1. Participant Input into Design

Participant involvement in the study design was obtained from 10 patients (6 in Italy, 1 in UK, and 3 in US [1 adolescent]) using 2 online qualitative surveys containing 17 questions over a period of 2 weeks. Based on the participant feedback, the following design elements will be implemented:

- Reduced number of laboratory samples and patient-reported outcomes (PRO) assessments
- A hybrid trial model, allowing for home visits and virtual/telemedicine visits at key assessments which will reduce the burden of onsite visits and offer some flexibility in visit timing for the participant's schedule

4.3. Justification for Dose

The dose rationale for this study is supported by the FTIH Study 205722 [GlaxoSmithKline Document Number 2019N411063_00] that investigated single SC doses of GSK3511294 ranging from 2 mg to 300 mg. The FTIH study was designed to collect robust blood eosinophil pharmacology data (including washout) in a relevant population (mild to moderate asthma and a blood eosinophil count ≥200 cells/µL at screening) and inform dose selection in late-phase development using Model-informed drug development (MIDD) principles [Wang, 2019; Marshall, 2019]. The precedence of using blood eosinophil reduction as a predictor of efficacy in severe asthma with an eosinophilic phenotype was established in two mepolizumab Phase 3 studies, which consistently reduced annualised exacerbation rate by approximately 50%, for associated reductions in blood eosinophils of 84% in the MENSA trial [Ortega, 2014] and 78% in the MUSCA trial [Chupp, 2017], compared with placebo. Since GSK3511294 targets the same IL-5 epitope as mepolizumab, establishing the same reduction in blood eosinophils

as mepolizumab via the same IL-5 neutralisation is expected to generate the same clinical efficacy in the same patient population (i.e., severe asthma with an eosinophilic phenotype with a previous history of two or more exacerbations in the past 12 months). In addition, given the precedented safety profile of IL-5 neutralisation comparable to placebo, targeting previous mepolizumab pharmacology is both valid and expeditious in selecting the dose of GSK3511294.

A comprehensive analysis of the clinical effects of GSK3511294 on blood eosinophils from Study 205722 was therefore conducted to identify the dose and frequency of dosing that match previous Phase 3 mepolizumab target pharmacology most closely. To this end, a Bayesian non-linear mixed-effects dose-time response model was used to analyse blood eosinophil data. This model was then used to calculate the posterior probability of achieving reductions of 78% for the MUSCA trial [Chupp, 2017] and 84% for the MENSA trial [Ortega, 2014] compared with placebo. Doses deemed suitable were defined as having a probability of exceeding MUSCA in excess of 80% while doses deemed unsuitable as having a probability of exceeding MENSA of less than 10%.

Based on the comprehensive analysis of the clinical effects of GSK3511294 on blood eosinophils, a dose of 100 mg SC GSK3511294 administered every 26 weeks has been selected to match the pharmacology seen with mepolizumab in two Phase 3 studies at the approved therapeutic dose, but over an extended period of 26 weeks [GSK Document Number 2019N418119_00].

4.4. End of Study and Study Completer Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed the visit at Week 52, regardless of whether the second dose of study intervention (at Week 26) was received.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if **all** of the following criteria apply:

AGE
1. **Age:** Adults and adolescents ≥12 years of age, at the time of signing the informed consent/assent. [For countries where local regulations or the regulatory status of study medication permit enrolment of adults only, participants recruited will be ≥18 years of age]
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. **Asthma:** Participants must have a documented physician diagnosis of asthma for ≥2 years that meets the National Heart, Lung, and Blood Institute guidelines [NHLBI, 2007] or GINA guidelines [GINA, 2020] **AND** a) **Eosinophilic phenotype:** Have, or with high likelihood of having, asthma with an eosinophilic phenotype as per Randomisation Criteria 1 and 2 (see Section 5.3) **AND** b) **Exacerbation history:** Have previously confirmed history of ≥2 exacerbations requiring treatment with systemic CS (IM, IV, or oral), in the 12 months prior to Visit 1, despite the use of medium to high-dose ICS (see criterion 4). For participants receiving maintenance CS, the CS treatment for the exacerbations must have been a two-fold dose increase or greater. 3. **Airflow obstruction:** Persistent airflow obstruction as indicated by: a) For participants ≥18 years of age at Visit 1, a pre-bronchodilator FEV_1 <80% predicted (NHANES III) recorded at Visit 1 b) For participants 12-17 years of age at Visit 1: • A pre-bronchodilator FEV_1 <90% predicted (NHANES III) recorded at Visit 1 **OR** • FEV_1:Forced Vital Capacity (FVC) ratio <0.8 recorded at Visit 1
ASTHMA MAINTENANCE THERAPY
4. **Inhaled Corticosteroid:** A well-documented requirement for regular treatment with medium to high dose ICS (in the 12 months prior to Visit 1 with or without maintenance OCS). The maintenance ICS dose must be ≥440 mcg FP HFA daily, or clinically comparable [GINA, 2020; see Appendix 10]. Participants who are

treated with medium dose ICS will also need to be treated with LABA to qualify for inclusion.

5. **Additional Controller Medication:** Current treatment with at least one additional controller medication, besides ICS, for at least 3 months [e.g., LABA, long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonist (LTRA), or theophylline].

SEX

6. **Male or eligible female.**

   Female Participants:

   - A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
     - Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4.1

       OR

     - Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4.2 from at least 14 days prior to the first dose of study intervention until at least 30 weeks after the last administered dose of study intervention.
   - A WOCBP must have a negative highly sensitive serum pregnancy test at screening Visit 1 and a negative highly sensitive urine pregnancy test within 24 hours before the first dose of study intervention. Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.
   - Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
   - The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated in relationship to the first dose of study intervention).
   - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

INFORMED CONSENT

7. **Informed Consent:** Capable of giving signed informed consent/assent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

French participants: In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

MEDICAL CONDITIONS

1. **Concurrent Respiratory Disease:** Presence of a known pre-existing, clinically important lung condition other than asthma. This includes (but is not limited to) current infection, bronchiectasis, pulmonary fibrosis, bronchopulmonary aspergillosis, or diagnoses of emphysema or chronic bronchitis (chronic obstructive pulmonary disease other than asthma) or a history of lung cancer.
2. **Eosinophilic Diseases:** Participants with other conditions that could lead to elevated eosinophils such as hyper-eosinophilic syndromes including (but not limited to) Eosinophilic Granulomatosis with Polyangiitis (EGPA, formerly known as Churg-Strauss Syndrome) or Eosinophilic Esophagitis.
3. **Parasitic infection:** Participants with a known, pre-existing parasitic infestation within 6 months prior to Visit 1.
4. **Immunodeficiency:** A known immunodeficiency (e.g. human immunodeficiency virus – HIV), other than that explained by the use of CSs taken as therapy for asthma.
5. **Malignancy:** A current malignancy or previous history of cancer in remission for less than 12 months prior to screening (Participants that had localised carcinoma of the skin which was resected for cure will not be excluded).
6. **Liver Disease:** Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice.

   NOTE: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) are acceptable if participant otherwise meets entry criteria.
7. **Other Concurrent Medical Conditions:** Participants who have known, pre-existing, clinically significant cardiac, endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.
8. **Vasculitis:** Participants with current diagnosis of vasculitis. Participants with high clinical suspicion of vasculitis at screening will be evaluated and current vasculitis must be excluded prior to enrolment.
9. **COVID-19:** Participants that, according to the investigator's medical judgment, are likely to have active COVID-19 infection should be excluded. Participants with known COVID-19 positive contacts within the past 14 days should be

excluded for at least 14 days following the exposure during which the participant should remain symptom-free.

PRIOR/CONCOMITANT THERAPY

10. **Monoclonal antibodies targeting IL-5/5R:** Participants who have received mepolizumab (Nucala), reslizumab (Cinqair/Cinqaero), or benralizumab (Fasenra) within 12 months prior to Visit 1 or who have a previous documented failure with anti-IL-5/5R therapy.
11. **Other mAbs in the treatment of asthma**: Participants who have received omalizumab (Xolair) or dupilumab (Dupixent) within 130 days prior to Visit 1.
12. **Other mAbs not used for the treatment of asthma:** Participants who have received any mAb within 5 half-lives of Visit 1.
13. **Investigational Medications:** Participants who have received treatment with an investigational drug within the past 30 days or five terminal phase half-lives of the drug whichever is longer, prior to Visit 1 (this also includes investigational formulations of marketed products).

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

14. **Previous participation:** Previously participated in any study with mepolizumab, reslizumab, or benralizumab and received study intervention (including placebo) within 12 months prior to Visit 1.

DIAGNOSTIC ASSESSMENTS

15. **ECG Assessment:** QTcF ≥450 msec or QTcF ≥480 msec for participants with Bundle Branch Block at screening Visit 1.

OTHER EXCLUSIONS

16. **Smoking history:** Current smokers or former smokers with a smoking history of ≥10 pack years (number of pack years = (number of cigarettes per day / 20) x number of years smoked). A former smoker is defined as a participant who quit smoking at least 6 months prior to Visit 1.
17. **Alcohol/Substance Abuse:** A history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1.
18. **Hypersensitivity:** Participants with allergy/intolerance to a mAb or biologic.
19. **Pregnancy:** Participants who are pregnant or breastfeeding. Participants should not be enrolled if they plan to become pregnant during the time of study participation. Requirements for pregnancy testing are located in Section 8.3.5.

20. **Adherence:** Participants who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations.

5.3. Randomisation Criteria

At the end of the run-in period, study participants must fulfil all of the randomisation inclusion/exclusion criteria below in order to be randomised to study intervention.

5.3.1. Randomisation Inclusion Criteria

RANDOMISATION INCLUSION CRITERIA

1. **Blood eosinophil count:**
   a) An elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past 12 months prior to Visit 1 that is related to asthma

      OR

   b) An elevated peripheral blood eosinophil count of ≥150 cells/μL at Screening Visit 1 that is related to asthma.
2. **Asthma:** Evidence of airway reversibility or responsiveness as documented by either:
   a) Airway reversibility (FEV_1≥12% and 200 ml) demonstrated at Visit 1 or Visit 2 using the Maximum Post Bronchodilator Procedure **OR**
   b) Airway reversibility (FEV_1≥12% and 200ml) documented in the 12 months prior to Visit 2 (randomisation visit) **OR**
   c) Airway hyperresponsiveness (methacholine: PC_{20} of <8 mg/mL, histamine: PD_{20} of <7.8 μmol, mannitol: decrease in FEV_1 as per the labelled product instructions) documented in the 12 months prior to Visit 2 (randomisation visit)
3. **eDiary compliance:** Compliance with completion of the eDiary defined as completion of all questions on 4 or more days out of the 7 days immediately preceding Visit 2.

5.3.2. Randomisation Exclusion Criteria

RANDOMISATION EXCLUSION CRITERIA

1. **Laboratory abnormality:** Evidence of clinically significant abnormality in the haematological, biochemical or urinalysis screen at Visit 1, as judged by the investigator.
2. **Liver chemistry test:** Participants who meet the following based on results from sample taken at Screening Visit 1:
   a) Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)

b) Total bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

c) Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice.

NOTES: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) is acceptable if the participant otherwise meets entry criteria.

3. **ECG:** Evidence of a clinically significant abnormality in the 12-lead ECG over-read conducted at Screening Visit 1, based on the evaluation of the investigator, **OR** QTcF ≥450msec or QTcF ≥480 msec for participants with Bundle Branch Block, at randomisation Visit 2.
4. **Unstable Asthma:** Participants with a clinically significant asthma exacerbation in the 7 days prior to randomisation should have their randomisation visit delayed until the investigator considers the participant's asthma to be stable (see Section 5.6).
5. **Maintenance Asthma Therapy:** Any changes in the dose or regimen of baseline ICS and/or additional controller medication (except for treatment of an exacerbation) during the run-in period.

5.4. Lifestyle Considerations

No lifestyle restrictions are required for this study.

5.5. Pre-screen/Screen/Run-in Failures

Pre-screen/screen/run-in failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any SAEs.

For the purposes of this study, pre-screen/screen/run-in failures will be defined as follows:

Pre-screen Failures	Screen Failures	Run-in Failures
Participants who are assigned a study number at the time of signing the informed consent (pre-screen visit) but do not progress to the screening visit.	Participants who complete at least one additional Visit 1 (Screening) procedure but do not enter the run-in period.	Participants who enter the run-in period but are not subsequently randomised.

Re-screening of participants will be permitted; however, advance written approval to proceed with re-screening a participant must be obtained from the Medical Monitor.

Re-screened participants should be assigned a new participant number for every screening/rescreening event.

5.6. Criteria for Temporarily Delaying Randomisation

Participants who experience a clinically significant asthma exacerbation during the run-in period should receive treatment for their exacerbation, have their randomisation visit delayed and remain in the run-in period (up to 6 weeks) until the investigator considers the participant to have returned to their baseline asthma status for at least 7 days.

A clinically significant exacerbation is defined as worsening of asthma requiring the use of systemic CS and/or hospitalisation and/or ED visit (Section 8.2.2).

A participant who is not eligible to continue in the study at the end of the run-in period, should be considered a run-in failure but may be rescreened after consultation with the Medical Monitor (Section 5.5).

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s)/product(s) (IP), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Study intervention will only be administered in the clinic; hence Visit 2 (Week 0) and Visit 10 (Week 26) are required to be in-clinic visits.

6.1. Study Intervention Administered

GSK3511294 is a humanised IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. GSK3511294 liquid drug product will be supplied by GSK in a Type I glass syringe (with a 1/2-inch, 29-gauge thin wall, staked needle and sealed with a latex-free rubber plunger). The drug product and syringe will be assembled in a single use, disposable safety syringe to enable delivery of the drug product. Each device enables SC delivery of 100 mg GSK3511294 in 1.0 mL sterile liquid formulation. The formulation contains L-histidine, trehalose dihydrate, L-arginine hydrochloride, disodium edetate (EDTA), water for injection and polysorbate 80.

The placebo in this study will be 0.9% sodium chloride solution contained in a PFS also supplied by GSK.

An overview of study intervention is provided in Table 2.

Table 2 Overview of Study Intervention

ARM Name	GSK3511294 100 mg	Placebo
Intervention Name	GSK3511294 100 mg SC	Placebo
Type	Biologic	N/A
Dose Formulation	Sterile liquid formulation in single-use PFS	Sterile 0.9% (w/v) sodium chloride solution in single-use PFS
Unit Dose Strength(s)	100 mg/mL; 1.0 mL (deliverable)	N/A, 1.0 mL (deliverable)
Dosage Level(s)	100 mg once every 26 weeks (Week 0 and Week 26)	Placebo once every 26 weeks (Week 0 and Week 26)
Route of Administration	SC injection	SC injection
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.

PFS=Pre-filled safety syringe, IMP=Investigational Medicinal Product, N/A=not applicable

6.1.1. Medical Devices

The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are injection devices:

- A pre-filled syringe contained within a safety syringe. The devices used in the study are representative of the devices planned to be marketed for the product.
- The components that comprise the pre-filled syringe (glass barrel with pre-staked needle and plunger) are sourced from Becton Dickinson. The pre-filled syringe is filled with study intervention (GSK3511294 or placebo) and assembled at GSK, Barnard Castle.
- The safety syringe components are manufactured by Becton Dickinson. The safety syringe components are assembled with the pre-filled syringe at GSK, Barnard Castle.

The Instruction for use (IFU) of the injection device will be provided. The instructions were developed and optimised as a result of formative human factors studies for mepolizumab and are representative of those that are planned for GSK3511294.

All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the investigator throughout the clinical investigation (see Section 8.4.8) and appropriately managed by GSK.

6.2. Packaging and Labelling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.3. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention.
- All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the SRM.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of

unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.4. Measures to Minimise Bias: Randomisation and Blinding

6.4.1. Treatment Assignment

- Eligible participants will be centrally randomised using an IRT system.
- The randomisation schedule will be generated using the GSK validated randomisation software RandAll NG. Separate randomisation schedules will be created for each country. Participants will be assigned to study intervention in accordance with the randomisation schedule. Once a randomisation number has been assigned to a participant, it cannot be reassigned to any other participant in the study.
- Randomisation will be stratified according to the participant's baseline ICS dose (medium [approximately 25% of participants] or high [approximately 75% of participants]; see Appendix 10).
- At Visit 2 (Week 0), those participants who meet the randomisation criteria will be randomised in a 2:1 ratio to receive one of the following study treatments in addition to their stable maintenance asthma treatment:
    - GSK3511294 100 mg SC
    - Placebo SC
- Study intervention will be administered in the clinic at Visit 2 (Week 0) and Visit 10 (Week 26) as per the SoA (Section 1.3).

6.4.2. Blinding

- The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.
- Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, GSK3511294 and placebo will be administered from PFSs that will be identical in appearance.

- If a participant's intervention code is unblinded by the investigator or treating physician, that participant will continue with all study visits but will not receive the second dose of study intervention at Week 26. The primary reason for the event or condition which led to the unblinding will be recorded in the CRF (see Section 7.1).
- To maintain the blind, haematology data (absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes) from post-randomisation samples will not be reported to the site or the central study team.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.5. Study Intervention Compliance

Both doses of GSK3511294 or placebo will be administered under medical supervision via SC injection to participants by the investigator or designee at the study site. Dose administration details (date and time) will be recorded in the source documents and reported in the CRF.

Participants will be monitored in clinic for a minimum of 2 hours post-dose to monitor for immediate hypersensitivity and any other untoward effects. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of GSK3511294, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care if appropriate.

6.6. Dose Modification

Dose modification is not allowed.

6.7. Continued Access to Study Intervention after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition whether or not GSK is providing specific post-study treatment.

At the end of the study, participants will be eligible to screen to enter the OLE Study 212895 and have continued access to open-label GSK3511294 if he/she:

- has received both doses of study intervention (at Week 0 and Week 26), AND
- completed the scheduled Exit Visit at Week 52, AND
- did not meet any of the study intervention discontinuation conditions (Section 7.1) during the study.

For participants who enrol into the 12-month OLE study, the Day 1 visit of the OLE study can occur on the same day as the Exit Visit of the current study. Specific details on the OLE study will be documented separately.

Participants who do not enter the OLE study will complete a follow-up visit/call and be prescribed alternative asthma therapy if needed and as determined by the study investigator.

6.8. Treatment of Overdose

The dose of GSK3511294 that is considered to be an overdose has not been defined. There are no known antidotes and there is no specific treatment for a suspected overdose. In FTIH study 205722 (refer to the current IB [GlaxoSmithKline Document Number 2016N295843_03 or later]), single SC doses of GSK3511294 up to 300 mg were well tolerated by adult participants with mild/moderate asthma (6 participants received a 300 mg SC dose).

Each PFS will enable the delivery of a single dose of study intervention (see Section 6.1). In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Treat the participant with active supportive care as dictated by the participant's clinical status in the knowledge of the long half-life (approximately 41 days) of GSK3511294.
- Closely monitor the participant for AE/SAE and laboratory abnormalities for 30 weeks following the last administered dose.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding discontinuation or delay of another dose of study intervention will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.9. Concomitant Therapy

At pre-screening and/or screening, information on the participant's baseline maintenance asthma therapy will be collected and recorded in the eCRF.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded in the eCRF along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency (any dose changes are to be recorded for OCS)

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Permitted Medications and Non-Drug Therapies

Throughout the study, participants are to be maintained on their baseline maintenance asthma treatment consisting of ICS plus at least one other controller, e.g. LABA, LAMA, with or without maintenance OCS (see inclusion criteria 4 and 5, Section 5.1). It is recognised that in a year-long study, changes may need to be individualised if clinically crucial for a participant. The investigator is encouraged to discuss any cases with the Medical Monitor before initiating changes to a participant's maintenance asthma medication.

Additional asthma medications such as theophyllines and anti-leukotrienes will be permitted provided that they have been taken regularly in the 3 months prior to screening (Visit 1). If uncertain whether a medication is permitted, please confirm with the Medical Monitor.

Albuterol/salbutamol is permitted throughout the study but should be withheld in the 6-hour period prior to spirometry assessments, if possible. Study-provided albuterol/salbutamol should not be recorded in the eCRF, only in the eDiary.

LABAs, LAMAs, and fixed dose combinations of ICS/LABA or ICS/LABA/LAMA should be withheld for ≥12 hours prior to spirometry, if possible.

Continuous Positive Airway Pressure (CPAP) or Bilevel Positive Airway Pressure (BiPAP) for the treatment of obstructive sleep apnoea is permitted, if initiated prior to the Screening Visit (Visit 1). This treatment must be captured in the eCRF.

Allergen-specific immunotherapy is permitted provided that it has been taken regularly in the 6 months prior to screening (Visit 1).

6.9.2. Prohibited Medications and Non-Drug Therapies

The following medications are not allowed prior to screening (Visit 1), according to the following schedule, or during the study:

Medication	**Washout Time Prior to Screening Visit**
Investigational drugs	1 month or 5 half-lives whichever is longer
Omalizumab [Xolair], dupilumab [Dupixent]	130 days
Mepolizumab [Nucala], reslizumab [Cinqair/Cinqaero], benralizumab [Fasenra]	12 months
Other monoclonal antibodies	5 half-lives
Experimental anti-inflammatory drugs (non biologicals)	3 months

Immunosuppressive medications such as those listed below (not all inclusive)
Corticosteroids if used to treat a condition other than asthma • Intramuscular, long-acting depot • Regular systemic (oral or parenteral)
Methotrexate, troleandomycin, cyclosporin, azathioprine
Oral gold
Chemotherapy used for conditions other than asthma

Additionally, Bronchial Thermoplasty and Radiotherapy are excluded for 12 months prior to Visit 1 and throughout the study. CPAP, BiPAP, and oxygen therapy should not be initiated during the run-in period.

6.9.3. Rescue Medicine

Trade label albuterol/salbutamol metered dose inhalers (MDIs) will be provided as rescue medication throughout the study. Albuterol/salbutamol will be sourced locally for all centres.

Participants will be dispensed an MDI at Screening Visit 1 to be used primarily to treat asthma symptoms on an as needed basis and also during the reversibility assessments (see Section 8.2.3.1). The MDI should be replaced as needed.

Although the use of rescue medications is allowable (at any time during the study), the use of rescue medications should be withheld, if possible, for at least 6 hours prior to the spirometry assessments. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the eDiary.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

No further doses of study intervention will be administered to participants who meet any of the following permanent treatment discontinuation conditions at any time during the study treatment period:

- Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria (see Section 7.1.1)
- ECG: Meets any of the protocol-defined QTc stopping criteria (see Section 7.1.2)
- Pregnancy: Positive pregnancy test (see Section 8.4.5)
- Severe allergic reaction/anaphylaxis: Participants with severe allergic reaction/anaphylaxis with no clear alternative cause (see Appendix 8)
- Vasculitis: Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation (see Section 7.5).
- Study treatment unblinded: Unblinding of the study treatment assigned to a participant (see Section 6.4.2).

If a participant meets any of the treatment discontinuation conditions or chooses (for any reason) not to receive another dose of study intervention before the end of the protocol specified randomised intervention period:

- The investigator will make every effort to encourage the participant to remain in the study **and** to continue with all remaining study visits, including the Exit and Follow-up Visits.
- The primary reason for discontinuation of study intervention (e.g., AE, lack of efficacy, protocol deviation, investigator discretion, consent withdrawn etc.) must be recorded in the eCRF.
- Participants will be provided with the option to continue their scheduled visits in-clinic, at home, or by phone. The required study assessments will depend on whether the participant is attending the visit in-clinic, at home, or by phone. At a minimum, an assessment of exacerbations, AEs, SAEs, and concomitant medications will be completed.
- If for any reason, the participant later chooses to withdraw from the study, a Withdraw from Study Visit (see Section 7.2) should be conducted according to the SoA (Section 1.3).

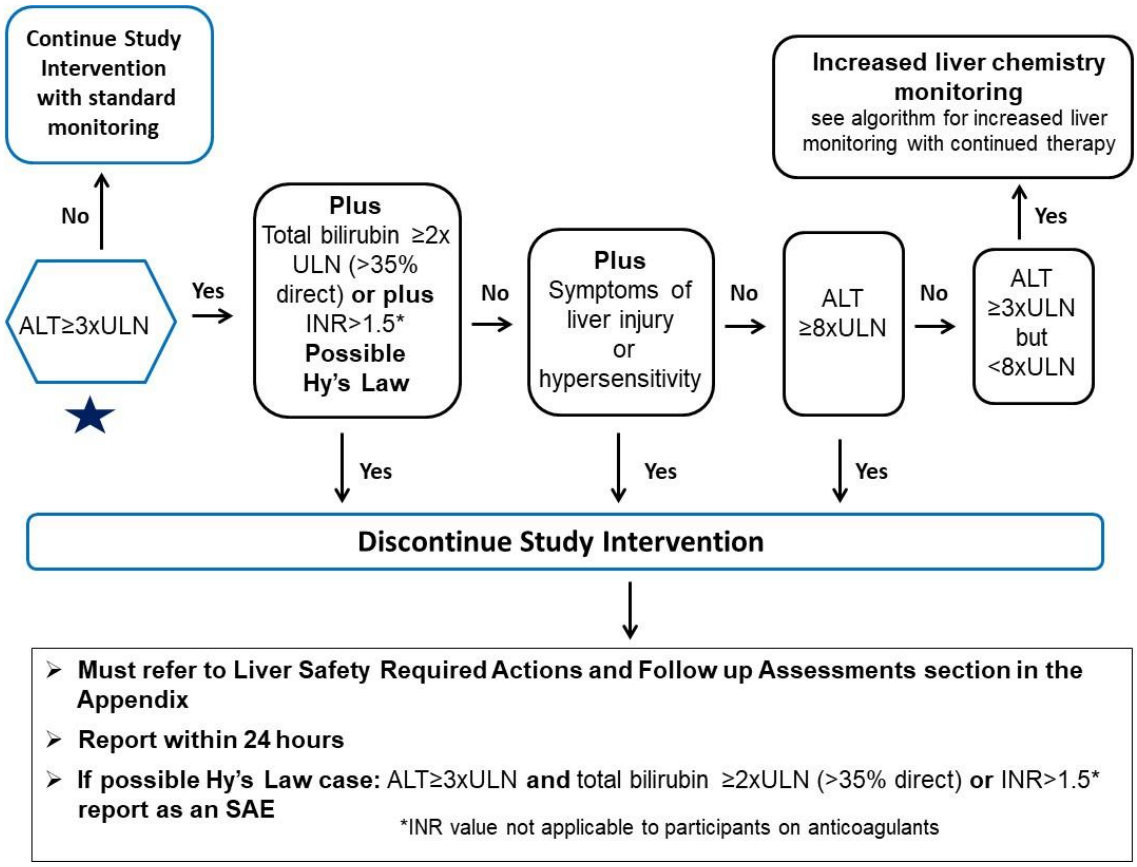
7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping criteria, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, the investigator believes that it is in the best interest of the participant.

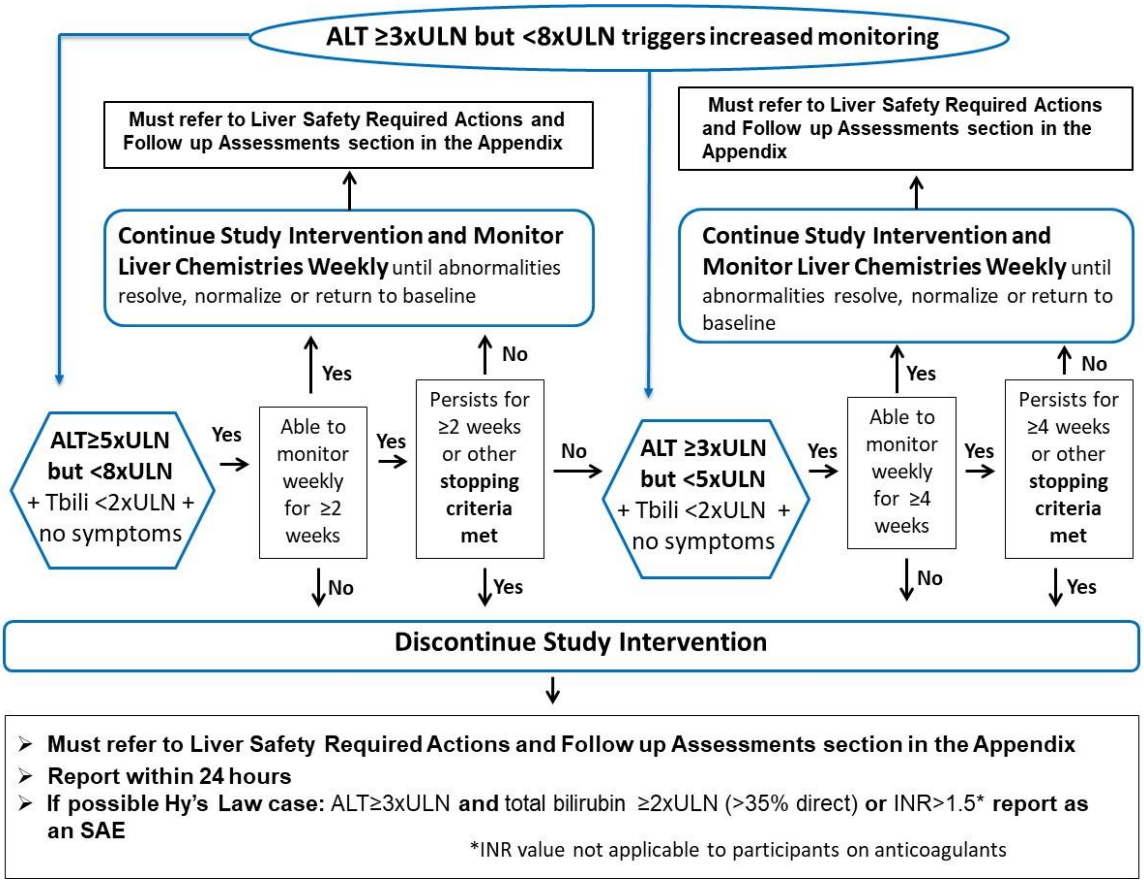
Liver Chemistry Stopping Criteria Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalised ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin

Refer to Appendix 6 for required Liver Safety Actions, Monitoring, and Follow-up Assessments.

Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT ≥3xULN but <8xULN and do not meet any of the liver stopping criteria



Abbreviations: ALT = alanine transaminase; Tbili = total bilirubin; INR = international normalised ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin.

Refer to Appendix 6 for required Liver Safety Actions, Monitoring and Follow-up Assessments.

7.1.1.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by a participant in this study will not be permitted.

7.1.2. QTc Stopping Criteria

Details on performing ECG assessments can be found in Section 8.3.3.

The QT interval corrected using Fridericia's formula (QTcF) must be used for *each individual participant* to determine eligibility for and discontinuation from the study intervention. This formula may not be changed or substituted once the participant has been enrolled.

For this study, the following QTc stopping criteria will apply:

- QTcF >500 msec OR uncorrected QT >600 msec
- Change from baseline of QTcF >60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTcF with Bundle Branch Block	**Discontinuation QTcF with Bundle Branch Block**
<450 msec	>500 msec
450 – 480 msec	≥530 msec

7.1.3. Temporary Discontinuation

For this study, a temporary discontinuation refers to a delayed administration of the second dose of study intervention at Week 26.

If a participant becomes infected (parasitic infection) during the study intervention period before receiving the second dose of study intervention and does not respond to anti-helminth treatment, a delayed administration of the study intervention may be considered in consultation with the GSK Medical Monitor.

7.2. Participant Discontinuation/Withdrawal from the Study

- Participants are strongly encouraged to remain in the study for the entire duration but may prematurely withdraw from the study at any time at his/her own request, at the request of their legally authorised representative (LAR), or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.
- Participants who prematurely withdraw from the study should attend:
  - a Withdraw from Study (WS) Visit, 26 weeks after the last administered dose of study intervention (at Week 26 or Week 52) **AND**
  - a Follow-up visit/call, 30 weeks after the last administered dose of study intervention for AE/SAE and pregnancy assessments.

  Note: this includes any participants who initially discontinue study intervention and remain in the study (Section 7.1) but later decide to withdraw from the study.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits (or scheduled phone calls, if applicable) and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study. A final attempt will be made to contact the participant for a safety follow-up 30 weeks after the last administered dose of study intervention.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

7.4. Reasons for Study Intervention Discontinuation and/or Study Withdrawal

The primary reason for study intervention discontinuation and/or study withdrawal will be recorded in the eCRF. When a participant withdraws consent, the investigator must document the reason (if specified by the participant) in the eCRF.

7.5. Criteria for Follow-up of Potential Type III Hypersensitivity (Immune Complex Disease /Vasculitis)

Owing to the adverse findings of arterial inflammation that were observed in the 1-month, but not 6-month, nonclinical toxicology studies, events potentially representing type III hypersensitivity/immune complex disease/vasculitis should be promptly reported to GSK, and consultation with the Medical Monitor is encouraged. Treatment for the event will be given as medically required. If possible, PK, ADA, C3, and C4 samples may be taken at the time of the event along with haematology, clinical chemistry and urinalysis.

Symptoms potentially suggestive of vasculitis include but are not limited to:

- persistent* fever (*where persistent is considered to be a duration of ≥2 days)
- persistent* muscle and joint pain

- persistent* rash
- persistent* fatigue
- symptoms of peripheral neuropathy, like numbness or weakness
- laboratory abnormalities, e.g., decreased platelets, elevated creatinine, decrease in complement C3/C4, abnormal urinary albumin/creatinine ratio

Participants who experience any of the above events should be monitored until the event resolves and/or a diagnosis is established.

The symptoms and clinical features are often non-specific and heterogenous with respect to the time course over which they develop, organ involvement and the constellation of symptoms and severity. Early recognition of potential events of vasculitis is important to timely diagnosis and subsequent treatment.

The precise management will depend on the clinical evaluation at the time of presentation and ongoing assessment including consideration of relevant differential diagnoses. Given that there is often a differential for presenting symptoms such as infection, and indeed such factors may also precipitate immune related AEs, these factors (infectious, neoplastic, metabolic, toxic) should be given due consideration and ruled out.

Serological, immunological, and histological (biopsy) data should be considered to support the diagnosis and consultation with the GSK Medical Monitor, and an appropriate medical specialist should be considered when investigating a possible immune related AE.

Unscheduled PK, ADA, C3 and C4 samples may be taken at the time of the event and samples may be taken for additional biomarkers (e.g., antinuclear antibodies [ANA], anti-neutrophil cytoplasmic antibodies [ANCA]) in the setting of clinical concern regarding the possibility of immune complex disease. If necessary, testing for biomarkers, e.g., ANA, ANCA (anti-myeloperoxidase [MPO] antibody and anti-proteinase 3 [PR3] antibody), may also be conducted using the frozen baseline serum samples (that were collected and stored prior to administration of study intervention) to allow for evaluation of interval change for participants with suspected vasculitis (see Section 8.7.2). Other possible causative or differential factors for abnormal clinical or laboratory observations may also have to be investigated including testing to exclude infection.

If clinically indicated, the participant may be referred to a specialist for further management, which may include organ biopsy.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Section 1.3).
- As detailed in the SoA (Section 1.3), participants who are not entering the OLE study 212895 should make every effort to complete the Week 56 follow-up visit/call on the scheduled day. The visit may be completed within 7 days of the scheduled time-point.
- Every effort should be made to reduce missing data throughout the study.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue to receive the second scheduled dose of study intervention, if applicable.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilised for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Laboratory results that could unblind the study (e.g., haematology differential [absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes]) will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Participants should be provided a quiet space in which to complete patient-reported outcomes (PRO), prior to other assessments and procedures. Site staff can provide limited advice if required, however participants should not be guided or directed in answering questions. Family or friends should not influence the answers. Site staff should encourage participants to complete all questions.

8.1. Screening and Critical Baseline Assessments

8.1.1. Pre-screening Visit (Visit 0)

Informed consent should be obtained at the Pre-screening Visit or the Screening Visit, prior to initiating any study assessments. A participant number will be assigned at the time the ICF is signed. Participants can conduct the Pre-screening Visit (Visit 0) up to 2 weeks prior to the Screening Visit (Visit 1).

The pre-screening procedures will include a review/assessment of:

- Inclusion/exclusion criteria (see Section 5.1 and Section 5.2)
- Demographic information including gender, ethnic origin, race, and year of birth (can be conducted at Visit 1 instead, if necessary)
- Childbearing status for all women (can be conducted at Visit 1 instead, if necessary); for WOCBP, contraception should be started at least 14 days prior to receiving the first dose of study intervention (see Appendix 4)
- Therapy history and concomitant medications including maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications

All clinic visits from Pre-screening Visit 0 to the Exit Visit (or if applicable, the WS Visit or the Follow-up Visit) must be registered in the IRT and the relevant eCRF form completed.

Serious adverse events must be collected from signing of Informed Consent if considered related to study procedures.

8.1.2. Critical Assessments performed at Screening (Visit 1)

The following critical assessments will be conducted at Screening Visit 1:

- Review inclusion/exclusion criteria (see Section 5.1 and Section 5.2)
- Review therapy history and concomitant medications including maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications.
- Medical history including:
  - Asthma including current treatment, duration of asthma, courses of rescue CSs, history of previous intubations, asthma exacerbation history in previous year, asthma triggers
  - Cardiovascular (CV) medical history/risk factors (as detailed in the eCRF)
  - Vasculitis, allergies and anaphylaxis history
  - Smoking history and current status
  - Historical blood eosinophil count - participants without a documented blood eosinophil count ≥300 cells/µL in the 12 months prior to Screening Visit 1 must show a blood eosinophil count ≥150 cells/µL, based on the sample collected at Visit 1 (see randomisation criterion 1, Section 5.3.1).
- Spirometry including bronchodilator responsiveness testing using the Maximum Bronchodilator Procedure (see Section 8.2.3)
- PGI-S (see Section 8.2.8)
- Safety Assessments including:
  - Physical exam (see Section 8.3.1)
  - Vital signs (see Section 8.3.2)

  - Resting 12-lead ECG (see Section 8.3.3)
  - AE/SAE assessment
- Blood/urine sample collection for the following laboratory tests (see Section 8.3.4):
  - Haematology with differential
  - Clinical chemistry (including liver chemistry)
  - Serum pregnancy test – for all WOCBP (childbearing potential for all women will be assessed at pre-Screening) (see Section 8.3.5)
  - Urinalysis (can be conducted at Visit 2 instead, if necessary)
  - Parasitic screening (only in regions with high-risk or for participants who have visited a high-risk region in the past 6 months)
- eDiary registration and training
- Provide medical problems and healthcare utilisation worksheet (see Section 8.9)
- Complete ADSD/ANSD (to be completed daily at home; see Section 8.2.10)

8.1.3. Critical Assessments performed at Randomisation (Visit 2)

The following critical assessments will be conducted at randomisation Visit 2:

- Review of randomisation criteria (see Section 5.3), and data collected at Visit 1, including, if applicable, verification that the asthma-related peripheral blood eosinophil count is ≥150 cells/μL, based on the sample collected at Visit 1
- Review of concomitant medications
- Spirometry (if airway reversibility was not demonstrated at Visit 1, the Maximum Bronchodilator Procedure may be repeated at Visit 2) (see Section 8.2.3)
- SGRQ (see Section 8.2.4)
- ACQ-5 (see Section 8.2.5)
- SNOT-22 (see Section 8.2.7)
- Review eDiary asthma symptoms and PEF summary report
- PGI-S (see Section 8.2.8)
- Safety assessments including:
  - Vital signs (see Section 8.3.2)
  - Resting 12-lead ECG (see Section 8.3.3)
  - AE/SAE assessment
- Blood/urine sample collection for the following laboratory tests (see Section 8.3.4):
  - Haematology with differential

- Total IgE
- Clinical chemistry (including liver chemistry)
- Urine pregnancy test – for all WOCBP (see Section 8.3.5)
- Complement C3 and C4
- PK (see Section 8.5)
- Baseline immunogenicity (see Section 8.8)
- Storage of a baseline sample that may be analysed for the presence of ANCA (anti-MPO antibody and anti-PR3 antibody tests), ANA, and anti-dsDNA antibody, if necessary (see Section 7.5)
- Storage of a baseline sample (with the participant's consent and where permitted) that may be analysed for exploratory biomarkers (see Section 8.7.3)

- Provide and review medical problems and healthcare utilisation worksheet (see Section 8.9)

The following items will be completed at home:

- PROMIS Items (see Section 8.2.6)
- Complete ADSD/ANSD daily (see Section 8.2.10)

8.2. Efficacy Assessments

8.2.1. Efficacy Endpoints

Efficacy endpoints and estimands are provided in Section 3.

8.2.2. Asthma Exacerbations

Clinically significant exacerbations of asthma are defined by:

Worsening of asthma which requires use of systemic CSs[1] and/or hospitalisation and/or Emergency Department (ED) visit.

[1]*For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.*

Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

Additional details on the process for determination of clinically significant exacerbations can be found in the Statistical Analysis Plan (SAP).

Details of each asthma exacerbation, including medications used to treat exacerbations should be recorded in the eCRF.

Asthma exacerbations should not be recorded as an AE unless they meet the definition of a SAE.

The time period for collection of exacerbation information in the eCRF will be from the start of study intervention until the Exit Visit or Follow-up Visit if applicable.

8.2.3. Pulmonary Function Testing/ Spirometry

Spirometry lung function assessments will be performed for all participants at specified visits to assess FEV_1. At least 3 valid spirometry efforts should be attempted (with no more than 8 attempts) using the ATS guidelines [Miller, 2005]. Spirometry includes FEV_1, percent predicted FEV_1, Forced Vital Capacity (FVC) and FEV_1/FVC. Spirometry assessments will be performed at screening (Visit 1), randomisation (Visit 2), and at scheduled in-clinic visits according to the SoA (Section 1.3). At each visit, spirometry should be performed at the same time of day (±1 hour) as the assessment performed at Visit 2 (the baseline assessment). Participants should try to withhold short-acting beta-2-agonists (SABAs) for ≥6 hours and LAMAs/LABAs for ≥12 hours prior to the clinic visit, if possible.

Spirometry should not be conducted for participants with confirmed/suspected COVID-19.

8.2.3.1. Reversibility using the Maximum Post-Bronchodilator Method

Pre-bronchodilator measurements will be taken at the clinic visits specified in the SoA (Section 1.3): at screening, randomisation, Week 26 Visit, and Exit Visit (or EW Visit). In addition, post-bronchodilator values will be recorded following reversibility testing using the Maximum Post-Bronchodilator Method. Participants' reversibility will be assessed at Visit 1 (Screening). For participants unable to achieve ≥12% reversibility and 200 mL change at Visit 1, reversibility can be repeated at Visit 2 to confirm eligibility for the study (see randomisation criterion 2, Section 5.3.1). The procedures involved in the Maximum Post-Bronchodilator Method are those generated by the Asthma Clinical Research Network. Additional details on the reversibility testing procedures using the Maximum Post-Bronchodilator Method can be found in the spirometry section of the third-party vendor manual.

8.2.4. St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a well-established instrument, comprising 51 questions designed to measure Quality of Life in participants with diseases of airway obstruction [Jones, 1992]. The questionnaire will be administered as per guidance from the measure developers and completed electronically according to the SoA (Section 1.3).

8.2.5. Asthma Control Questionnaire-5 (ACQ-5)

The ACQ-5 is a five-item questionnaire, which has been developed as a measure of participants' asthma control that can be quickly and easily completed [Juniper, 2005]. The questions are designed to be self-completed by the participant. The five questions enquire about the frequency and/or severity of symptoms (nocturnal awakening on

waking in the morning, activity limitation, and shortness of breath, wheeze) over the previous week. The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. This will be completed electronically according to the SoA (Section 1.3).

8.2.6. PROMIS Fatigue Items

The PROMIS Fatigue Item Bank includes a number of items assessing concepts from mild tiredness to exhaustion [Christodoulou, 2008; Cella, 2016]. A small number of individual questions assessing the concept of "Energy" from the PROMIS Fatigue item bank will be administered. Participants will complete these items on an electronic handheld device.

The PROMIS fatigue items should only be administered to participants for whom an appropriate translation is available (see the SRM for further details).

8.2.7. Sino-nasal Outcomes Test-22 (SNOT-22)

The SNOT-22 is a 22-item self-administered questionnaire to measure disease-specific quality of life of chronic rhinosinusitis (with or without nasal polyposis). The SNOT-22 contains questions about a broad range of health and HRQoL problems including physical problems, functional limitations and emotional consequences. The questions are designed to be self-completed by the participant [Hopkins, 2009]. The participant is asked to rate the severity of each item over the previous 2 weeks on a scale from 0 (no problem) to 5 (problem as bad as it can be). Responses to the questionnaire will be captured electronically.

The SNOT-22 questionnaire should only be administered to participants for whom an appropriate translation is available (see the SRM for further details).

8.2.8. Patient Global Impression of Asthma Severity/Change (PGI-S, PGI-C)

Patient Global Impression of Asthma Severity (PGI-S): The participant will complete a PGI-S question at Randomisation and visits according to the SoA (Section 1.3). This single global question will ask participants to rate their asthma severity on a five-point scale (no symptoms, mild, moderate, severe, very severe). Responses will be captured electronically.

Patient Global Impression of Change (PGI-C) from Baseline of Asthma Severity: The participant will complete a PGI-C question from baseline of their asthma severity at the visits specified in the SoA (Section 1.3). The single question will ask participants to rate the overall change in their asthma severity compared with Day 1 (randomisation) prior to start of study intervention. The rating will use a five-point scale (much better, a little better, no change, a little worse, much worse) and responses will be captured electronically.

Additional instructions will be provided in the SRM.

8.2.9. Clinician/Patient Rated Response to Therapy

This is an overall evaluation of response to treatment, conducted separately by the investigator and the participant using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse

The evaluations will be completed electronically at the visits specified in the SoA (Section 1.3).

8.2.10. Asthma Daily Symptom Diary/Asthma Nightly Symptom Diary (ADSD/ANSD)

The ADSD/ANSD is a 6-item self-administered patient-reported diary developed by the PRO Consortium's Asthma Working Group (in accordance with the Food and Drug Administration's PRO Guidance) to facilitate comprehensive and reliable assessment of asthma symptoms from a patient's perspective [Gater, 2016].

The ADSD/ANSD is intended for use by adults and adolescents (aged 12 years and older) who are diagnosed with asthma to rate the severity of their symptoms in the three core categories: breathing symptoms (wheezing, shortness of breath), chest symptoms (chest tightness, chest pain) and cough.

The ADSD/ANSD must be completed twice daily by the participant:

- The morning diary (ADSD) is to be completed upon waking and refers to asthma symptoms during the night-time.
- The evening diary (ANSD) is to be completed before going to bed and refers to asthma symptoms during the day.

Participants are required to rate the six symptoms at their worst during the respective timeframes using an 11-point numeric rating scale (NRS) ranging from 0 ('None') to 10 ('As bad as you can imagine'). Responses will be captured electronically.

Further details are contained in the SRM.

8.2.11. eDiary Asthma Parameters and Alerts

The participant will be asked to record the following parameters daily in the eDiary from Visit 1 onwards:

- Morning peak expiratory flow (best of three), before rescue medication usage (L/min).
- Occasions of rescue usage over the previous 24-hours.

- Asthma symptom score over the previous 24-hours using a 6-point scale (Appendix 9).
- Frequency of awakening due to asthma symptoms requiring rescue medication use.

For safety the following alerts, indicative of worsening asthma, will be programmed into the eDiary with instructions to contact the investigator if any of the alert criteria are met. An alert in itself will not qualify as a clinically significant exacerbation:

- Decrease in morning PEF ≥30% on at least two of three successive days, compared with baseline (last 7 days of run-in).
- An increase of ≥50% in rescue medication on at least two of three successive days, compared with the average use for the previous week.
- Awakening due to asthma symptoms requiring rescue medication use for at least two of three successive nights.
- A symptom score of 5 for at least two of three successive days.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3) – where possible, these should be aligned with standard of care.

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Eyes, CV, Respiratory, Gastrointestinal and Neurological systems. Height (screening only) and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

- Oral or skin temperature, pulse rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the resting state with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and should be taken before blood collection for laboratory tests.

8.3.3. Electrocardiograms (ECGs)

- Twelve-lead ECGs will be obtained at the time points specified in the SoA (see Section 1.3) using an ECG machine, provided by GSK via a designated central laboratory, that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

- The QTcF formula must be used for *each* individual participant to determine eligibility. This formula may not be changed or substituted once the participant has been enrolled. Refer to Section 7.1.2 for the QTcF formula.
- If a routine ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTcF values of the three ECGs to determine whether the participant should be discontinued from the study intervention (but not from the study). Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- ECG measurements will be made after the participant has rested in the supine position for 5 minutes. The ECG should be obtained after the vital signs assessments but before lung function testing followed by other study procedures. Collection shortly after a meal or during sleep should be avoided since QT prolongation can occur at these times.
- Paper ECG traces will be recorded at a standard paper speed of 25 mm/sec and gain of 10 mm/mV, with a lead II rhythm strip. There will be electronic capture and storage of the data by a validated method.
- Paper ECG traces are required to be maintained at the site with other source documents.

8.3.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and refer to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study until the Exit Visit (or Follow-up visit/call if applicable) should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or Medical Monitor. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the Sponsor notified.
- If laboratory values from non-protocol specified laboratory tests performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

- To maintain the treatment blind, the site and the central study team will not be sent information on haematology differential (absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes) from any visits post-randomisation.

8.3.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- A serum pregnancy test should be conducted for all WOCBP at the screening visit (Visit 1) and the Exit visit. In addition, a urine pregnancy test should be performed for all WOCBP prior to randomisation (Visit 2), on a monthly basis at the specified scheduled study visit, and at the Follow-up Visit/call (if applicable) as per the SoA (Section 1.3).
- A final urine pregnancy test should be conducted for all WOCBP, 30 weeks after the last administered dose of study intervention:
    - Participants who enter the OLE study will have a urine pregnancy test prior to receiving the first dose of open-label GSK3511294.
    - Participants who do not enter the OLE study should have a urine pregnancy test at the Follow-up Visit/call (Week 56). A self-reported home urine pregnancy test result is acceptable if the follow-up is conducted as a phone call visit.
    - Participants who withdraw early from the study should have a urine pregnancy test, 4 weeks after the WS Visit (see Section 7.2).
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Section 10.3. Asthma exacerbations should not be recorded in the AE section of the eCRF unless they meet the definition of a SAE.

The definitions of device-related safety events, (adverse device effects [ADEs] and serious adverse device effects [SADEs]), can be found in Section 10.7. Device deficiencies are covered in Section 10.7.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of intervention (Visit 2) until the Exit Visit or follow-up visit/call (if applicable) at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the Exit Visit or the follow-up visit/call (if applicable) at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions (in the eCRF) not as AEs.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to GSK within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify GSK.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 8.4.7), will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to GSK of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from GSK will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and GSK policy and forwarded to investigators as necessary.

8.4.5. Pregnancy

- Any female participant who becomes pregnant while participating in the study will not receive another dose of study intervention.
- Details of all pregnancies in female participants will be collected from the start of study intervention and until 30 weeks after the last administered dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within **24 hours** of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.4.6. Cardiovascular and Death Events

For any CV events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV CRF pages are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific CV section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF page is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.4.7. Adverse Events of Special Interest

Adverse events of special interest (AESI) include:

- Allergic reactions including anaphylaxis

  Note: these events will be assessed by the investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006] (Appendix 8).

- Type III hypersensitivity (immune complex disease/vasculitis) reactions
- Local injection site reactions
- QTc prolongation

See Section 2.3.1 for additional details.

8.4.8. Medical Device Deficiencies

Medical devices (PFS) are being provided for use in this study as a delivery method for GSK3511294 or matching placebo injections. To fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device Deficiency can be found in Section 10.7.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 10.3 of the protocol.

8.4.8.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- The method of documenting Medical Device Incidents is provided in Section 10.7.

8.4.8.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study.

- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.8.3. Prompt Reporting of Medical Device Deficiencies to Sponsor

- Device deficiencies will be reported to the Sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.
- The Medical Device Deficiency Report Form will be sent to the Sponsor by email. If email is unavailable, then fax should be utilised.
- The Sponsor will be the contact for the receipt of device deficiency reports.

8.4.8.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all deficiencies occurring with any medical device provided for use in the study in order for the Sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.5. Pharmacokinetics

- Blood samples will be collected for measurement of plasma concentrations of GSK3511294 as specified in the SoA (Section 1.3).
- The actual date and time (24-hour clock time) of each sample will be recorded. Samples obtained at Visit 2 (Week 0) and Visit 10 (Week 26) should be drawn prior to dosing.
- Collection, processing, storage and shipping procedures are provided in the central laboratory manual.
- Intervention concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6. Genetics and Pharmacogenomics

China only: Genetic blood samples will **not** be collected from participants in China.

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is

optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Section 10.5. Genetics and Pharmacogenomics for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the central laboratory manual.

8.7. Biomarkers/ Pharmacodynamic Markers

8.7.1. Blood Eosinophil Counts

In order to investigate the PD effects of GSK3511294, blood eosinophil counts will be measured as part of the standard haematological assessments according to the SoA (Section 1.3). The site staff and central study team will be blinded to each participant's blood eosinophil count (as well as overall haematology differential [absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes]) from all post-randomisation blood tests. Total white blood cell counts will be available throughout the study.

8.7.2. Complement, IgE, and Inflammatory Markers

Blood samples will be collected to measure complement (C3 and C4) and total IgE, according to the SoA (Section 1.3).

A baseline serum sample will be collected at Visit 2 and stored. If necessary, this sample may be analysed for the presence of ANCA (using anti-MPO antibody and anti-PR3 antibody tests), and ANA, including anti-dsDNA antibodies. After dosing, additional inflammatory markers and tests may be considered on an ad-hoc basis should there be clinical concerns regarding an immune-mediated AE (see Section 7.5).

8.7.3. Exploratory Biomarkers

China only: Blood samples for exploratory biomarkers will **not** be collected from participants in China.

With the participant's consent and where permitted, a serum sample for exploratory biomarkers will be collected as specified in the SoA (Section 1.3). The samples will be stored after collection and may be analysed for any biomarkers that are thought to play a role in GSK3511294 response, asthma or related diseases, or to evaluate their association with observed clinical responses to GSK3511294. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to GSK3511294.

Participation in exploratory biomarker research is optional. Participants who do not wish to participate in the exploratory biomarker research may still participate in the study.

8.8. Immunogenicity Assessments

Antibodies to GSK3511294 will be evaluated in serum samples collected from participants according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the Exit Visit or the final in-clinic visit for participants who withdraw early from the study. Processing, storage and shipping procedures are provided in the SRM.

In the immunogenicity assessment for GSK3511294, a tiered analyses approach will use a validated binding ADA assay (screening, confirmation and titration assays) and a validated neutralisation antibody (NAb) assay. If necessary, further immune response characterisation may be performed as needed.

8.9. Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation data, associated with medical encounters, will be collected by the investigator and study-site personnel for all participants throughout the study. The data will be collected using a medical problems and healthcare utilisation worksheet according to the SoA (Section 1.3). Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to evaluate the effect of GSK3511294 on health care resource utilisation for asthma including hospitalisation, ED visits, and physician office/clinic visits.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary study objective is to test for the superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC, assessed by the annualised rate of clinically significant exacerbations measured over the study intervention period of 52 weeks.

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 and placebo.

9.2. Sample Size Determination

Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125).

9.2.1. Sample Size Assumptions

A sample size of 375 participants (2:1 GSK3511294 to placebo allocation ratio) is based on sufficient power to conclude superiority on primary and key secondary endpoints.

9.2.1.1. Primary Endpoint

The assumed true annualised rate of exacerbations in the placebo arm is 1.18. Based on an assumed true treatment difference of a 50% reduction in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC, a sample size of 375 randomised participants (250 to GSK3511294, 125 to placebo) will provide 99% power for the primary endpoint at a 5% two-sided significance level [PASS, 2020].

The assumptions for the placebo rate and treatment effect are median values from an elicitation exercise which used Phase 3 anti-IL-5/5R historical data (~50% reduction in exacerbations) and expert opinion. The sample size is based also on an assumption of 0.8 for the dispersion parameter which was observed in two mepolizumab studies [Pavord, 2012; Ortega, 2014]. It was assumed that 14% of participant-years data will be missing due to study withdrawal, which is also consistent with mepolizumab studies.

Based on the assumptions above, the minimum observed treatment difference estimated to result in significance at the 5% two-sided significance level is a 27% reduction in exacerbations for GSK3511294 + SoC compared with placebo + SoC (rate ratio of 0.73).

9.2.1.2. Secondary Endpoints

Table 3 describes the assumptions and power values for two key secondary endpoints. The assumptions are obtained from the Phase 3 mepolizumab studies [Pavord, 2012; Ortega, 2014; Chupp, 2017].

Table 3 Power Calculations for Key Secondary Endpoints

Endpoint	Assumed treatment difference (GSK3511294 + SoC vs. placebo + SoC)	Standard deviation	Power
Change from baseline in SGRQ total score at Week 52	-7	17	96%
Change from baseline in ACQ-5 score at Week 52	-0.35	1.1	83%

9.2.2. Sample Size Sensitivity

The sample size and power calculations are based on assumptions about the true values for parameters. The power of the study is dependent on changes in these assumptions, in particular the assumed annualised exacerbation rates. Table 4 illustrates how changes in assumptions for two parameters (placebo + SoC annualised exacerbation rate and treatment effect) affect the power.

Table 4 Estimates of Power for Assumed Placebo + SoC Exacerbation Rate and Assumed Percent Reduction with GSK3511294 + SoC Compared with Placebo + SoC

Percent reduction in annualised exacerbation rate with GSK3511294 + SoC vs. placebo + SoC	Placebo + SoC annualised exacerbation rate			
	1.0	1.1	**1.18**	1.3
30%	61	63	65	67
40%	88	90	91	92
50%	98	99	**99**	99

9.2.3. Sample Size Re-estimation or Adjustment

There will be no sample size re-estimation.

There is a possibility for randomising greater than 375 participants in the study. This is due to local country requests or requirements, for example, the local health authority specifying a minimum number to be enrolled. The primary analysis and clinical study report (CSR) will be based on the initial target enrolment. If the study target enrolment is reached before a local country enrolment requirement is met, then recruitment in that country may continue. Participants from those countries, who have already been enrolled at the time of reaching the target enrolment, will be included in the primary analysis. All data (pre- and post-target enrolment) will be analysed together but reported later in a supplement to the study report. Inferences will be drawn on the original study report based on the target enrolment.

9.3. Analysis Sets

For the purpose of analyses, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF and for whom a record exists.
Safety	All randomised participants who receive at least one dose of study intervention. Participants will be analysed according to the study intervention they actually received.
Modified Intent-to-Treat (mITT)	All randomised participants who receive at least one dose of study intervention. This population will serve as the primary population for analyses of efficacy endpoints and will utilise the actual intervention received.

All further populations to be used for the assessment of biomarker, PK, and health resource use will be defined in the SAP.

9.4. Statistical Analysis

The SAP will be finalised prior to un-blinding and it will include a more technical and detailed description of the statistical analyses described in this section.

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC.

9.4.2. Primary Endpoint

9.4.2.1. Main Estimand

Target Participant Population	Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.
Primary Endpoint	Annualised rate of clinically significant exacerbations over 52 weeks. Clinically significant exacerbations are defined in Section 8.2.2.
Intercurrent events and strategies	The anticipated key intercurrent events and corresponding strategies are: a) Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring

	b) Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred c) Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring
Summary measure	Ratio of the rates of exacerbations between GSK3511294 + SoC and placebo + SoC.
Analysis Method	The primary analysis of the annualised rate of clinically significant exacerbations will use a negative binomial model. Covariates included will be baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high dose, see Appendix 10), region, number of exacerbations in the year prior to the study, baseline % predicted FEV_1 and treatment group with $\log_e$(time in study in years) as an offset variable. The rate ratio and 95% confidence interval (CI) will be provided for the comparison between GSK3511294 + SoC and placebo + SoC.
Handling of missing data and intercurrent events leading to exclusion of data	Missing data or data excluded due to intercurrent events will be handled as follows: a) For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed "missing at random" (MAR) (based on all data included in the analysis under the current estimand strategy). b) For participants that withdraw from the study, preventing assessment of the primary endpoint, the data for the period following withdrawal will be assumed MAR (based on all data included in the analysis under the current estimand strategy). **Sensitivity analyses** will be conducted to investigate the conclusions from deviations from these assumptions regarding missing data for (b) above. Missing data for participants will be based on data from participants who have discontinued study intervention (off-treatment) but remained in the study [Roger, 2019]. A tipping point analysis will also be conducted that will impute missing data based on a plausible range of values for the rate of exacerbations per year. The imputed exacerbation rates will be varied independently for treatment arms. Further details will be provided in the SAP.

9.4.3. Secondary Endpoints

9.4.3.1. Main Estimands

Target Participant Population	Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.
Secondary Endpoints	• Change from baseline in SGRQ total score at Week 52 • Change from baseline in ACQ-5 score at Week 52

	• Change from baseline in pre-bronchodilator FEV_1 at Week 52
Intercurrent events and strategies	The anticipated key intercurrent events and corresponding strategies: a) Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring. b) Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred. c) Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring
Summary measure	Difference in means between GSK3511294 + SoC and placebo + SoC.
Analysis Method	The analysis will be performed using a repeated measures mixed model. Covariates included will be baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high dose, see Appendix 10), number of exacerbations in the year prior to the study, baseline % predicted FEV_1,treatment group and visit, plus interaction terms for visit by baseline and visit by treatment group. The difference in means and 95% CI will be provided for the comparison between GSK3511294 + SoC and placebo + SoC.
Handling of missing data and intercurrent events leading to exclusion of data	Missing data or data excluded due to intercurrent events will be handled as follows: a) For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). b) For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy). **Sensitivity analyses** will be conducted to investigate the conclusions from deviations from these assumptions regarding missing and excluded data for (b) above. Missing data for participants will be based on data from participants who have discontinued study intervention (off-treatment) but remained in the study [Roger, 2019]. A tipping point analysis will also be conducted that will impute missing data based on a plausible range of means. The imputed means will be varied independently for treatment arms. Further details will be provided in the SAP.

The annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks will be evaluated using the same strategy as that described for the primary endpoint (see Section 9.4.2).

9.4.4. Other Endpoints

Full details of analysis methods to be used for other endpoints will be provided in the SAP.

9.4.5. Safety Analyses

All safety analyses will be performed on the Safety Population. Summaries of data will report data according to the nominal visit for which it was recorded. Occurrence of AEs, SAEs, AESIs, laboratory data, vital signs, and ECGs will be included in data displays in the form of listings, frequency tables, summary statistics, graphs, and statistical analyses where appropriate.

Adverse Events (AEs) will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and will be grouped by system organ class (SOC). AEs will be summarised by frequency and percentage of participants, by SOC and preferred term within each treatment group. Separate summaries will be presented for all AEs, drug-related AEs, serious AEs (SAEs), AEs leading to permanent discontinuation of study intervention or withdrawal from study and for any AEs of special interest.

9.5. Multiple Testing Strategy

The treatment comparison of interest for the primary and secondary endpoints is GSK3511294 100 mg SC + SoC vs placebo + SoC. A fixed sequence hierarchical testing procedure will be used to provide strong control of Type I error for multiplicity arising from the primary and multiple secondary endpoints. This will be carried out using a stepdown closed testing procedure where inference for an endpoint in the predefined hierarchy will be dependent on statistical significance having been achieved for the previous endpoints in the hierarchy. For example, for the primary endpoint, GSK3511294 + SoC will be compared to placebo + SoC at a two-sided 5% level. The next endpoint in the hierarchy (i.e. the first secondary endpoint) will be tested only if the test for the primary endpoint is significant at the two-sided 5% level. Testing will continue down the hierarchy for the remaining endpoints in an equivalent manner only if the previous endpoint in the hierarchy achieves statistical significance.

The hierarchy of the primary and secondary endpoints to be tested is as follows:

1. Annualised rate of clinically significant exacerbations over 52 weeks
2. Change from baseline in SGRQ at Week 52
3. Change from baseline in ACQ-5 at Week 52
4. Change from baseline in clinic pre-bronchodilator FEV_1 at Week 52
5. Annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

9.6. Interim Analysis

No interim analyses are planned.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide GSK with sufficient, accurate financial information as requested to allow GSK to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or their legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- For participants 12-17 years old, written informed assent must be obtained in addition to the legally authorised representative(s)' consent. Assent will be obtained in accordance with applicable country or IRB/Ethics Committee regulations. Written informed consent will be obtained from participants turning 18 years of age to continue participation in the study.
- The medical record must include a statement that written informed consent/assent was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorised person obtaining the informed consent/assent must also sign the ICF.
- Participants must be re-consented/re-assented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorised representative.

Participants who are rescreened are required to provide consent/assent and sign a new ICF/assent form.

GSK (alone or working with others) may use a participant’s coded study data and samples and other information to carry out this study; understand the results of this study; learn more about GSK3511294 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have GSK3511294 approved for medical use or approved for payment coverage.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by GSK. Any participant records or datasets that are transferred to GSK will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by GSK in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by

GSK, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

An Independent Data Monitoring Committee (IDMC) comprised of clinical experts external to GSK will review unblinded data at defined timepoints during the study. If deemed appropriate by the IDMC, or upon request by GSK or investigators, additional timepoints for review may be added.

Details of the structure and function of the IDMC, and analysis plan for IDMC reviews, are outlined in the IDMC Charter, which is available upon request.

In addition to the IDMC, the GSK SRT will review blinded safety data at regular intervals throughout the study to ensure participant safety, which includes safety signal detection at any time during the study. Details of the SRT process will be available in relevant SRT documents. The SRT will inform the IDMC if any safety signals are identified.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymised participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymised patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- GSK or a designee is responsible for the data management of this study including quality checking of the data.
- GSK assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of GSK. No records may be transferred to another location or party without written notification to GSK.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records

or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or

suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- GSK will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, GSK will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

All protocol required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).

Local laboratory results may be required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation to be performed – for example: when results from screening Visit 1 should be available before dosing on Visit 2, or at any time when a participant is unwell and results are required urgently.

If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded in the CRF.

To maintain the blind, the following data for post-randomisation samples will not be reported to investigators and blinded Sponsor representatives: absolute and percentage values of eosinophils, neutrophils, lymphocytes, monocytes, and basophils.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Haematology[1]	Platelet Count	<u>*RBC Indices:*</u>	<u>*WBC count with Differential:*</u> *(post-dose results blinded as described in footnote 1)*	
	RBC Count	MCV	WBC	
	Haemoglobin	MCH	Neutrophils	
	Haematocrit	%Reticulocytes	Lymphocytes	
			Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry[2]	BUN	Potassium	AST(SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase[3]	Albumin
		Magnesium		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination and UACR (if blood or protein is abnormal [evidence of microalbuminuria or haematuria of ≥1+])			
Pregnancy testing	• Highly sensitive serum pregnancy test at Screening Visit 1 and Exit Visit; urine pregnancy tests for all other scheduled visits (as needed for WOCBP)[4]			
Other Screening Tests	• FSH and oestradiol (if required to confirm postmenopausal status) • Parasitic Screening (only required in regions with high-risk or for participants who have visited high-risk regions in the past 6 months). Sites should use local laboratories. • Total IgE • Serum samples collected at baseline will be frozen and stored for later analyses, if necessary: anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			

NOTES:
ALT = Alanine Aminotransferase; ANA = anti-nuclear antibody; AST = Aspartate Aminotransferase; BUN = Blood urea nitrogen; FSH = Follicle-stimulating hormone; MPO=myeloperoxidase; PR3=proteinase 3; SGOT = Serum Glutamic-Oxaloacetic Transaminase; SGPT = Serum Glutamic-Pyruvic Transaminase; UACR = urinary albumin-creatinine ratio; WBC = white blood cell; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

1. To maintain the treatment blind, the following data for post-randomisation samples will not be reported to investigators and blinded Sponsor representatives: absolute and percentage values of eosinophils, neutrophils, lymphocytes, monocytes, and basophils.
2. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.6 All events of ALT ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalised ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported to GSK as an SAE.
3. If alkaline phosphatase is elevated, consider fractionating.
4. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalisation for signs/symptoms of the disease under study, death due to progression of disease, etc.).

An SAE is defined as any serious adverse event that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation • In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AE. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalised ratio (INR) >1.5 must be reported as SAE
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours and send/fax it to the Medical Monitor.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to study intervention/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor or the SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Medical monitor or the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.
- Permanent sterilisation methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female
   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   a) A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   b) Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance:

Female participants:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)c
• Bilateral tubal occlusion
• Azoospermic partner (vasectomised or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

• Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulationc
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulationc
  • oral
  • injectable

• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

Male participants: As GSK3511294 is a mAb that is not anticipated to interact directly with deoxyribonucleic acid (DNA) or other chromosomal material and minimal exposure through semen is expected, male participants will not be required to use contraception during the study.

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

China only: No genetic samples will be collected from participants in China.

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK3511294 or asthma with an eosinophilic phenotype and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3511294 or study interventions of this drug class, and indication. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- Additional analyses of DNA samples may be conducted if it is hypothesised that this may help further understand the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to GSK3511294 or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3511294 (or study interventions of this class) or asthma with an eosinophilic phenotype continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Required Actions, Monitoring and Follow-up Assessments

Liver Chemistry Stopping Criteria and Increased Monitoring Criteria are designed to assure participant safety and evaluate liver event aetiology.

Liver Chemistry Stopping criteria and Required Follow-up Assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥ 8xULN</td></tr>
<tr><td>ALT Increase</td><td colspan="2">ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
ALT ≥ 3xULN but <5xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td colspan="2">ALT ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td colspan="2">ALT ≥ 3xULN and INR>1.5</td></tr>
<tr><td>Cannot Monitor</td><td colspan="2">ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks
ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td colspan="2">ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="3">Required Actions, Monitoring and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th colspan="2">Follow-Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform follow-up assessments as described in the Follow-up Assessment column.
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5:</td><td colspan="2">• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, within a week of meeting increased liver monitoring criteria.[5]
• Obtain a serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin.
• Fractionate bilirubin, if total bilirubin≥2xULN</td></tr>
</table>

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **For all other stopping criteria (total bilirubin <2xULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilise or return to within baseline **RESTART/RECHALLENGE** • **Do not restart/rechallenge** participant with study intervention since **it is not allowed per protocol;** continue participant in the study for any protocol specified follow-up assessments.	• Obtain complete blood count with differential to assess eosinophilia. This blood sample will be sent to the central laboratory to maintain the blind while study is ongoing. Results will be provided only if unblinding of a participant's treatment assignment is required. Also note that the mechanism of action of GSK3511294 leads to lowering of eosinophils. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications. • Record alcohol use on the liver event alcohol intake form **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease; complete Liver Imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance:

	○ In patients when serology raises the possibility of autoimmune hepatitis (AIH) ○ In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention ○ In patients with acute or chronic atypical presentation: • If liver biopsy conducted complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3xULN and total bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5 which may indicate severe liver injury (possible 'Hy's Law'), **must be reported to GSK as an SAE**; the INR threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: hepatitis A Immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal, 2005].
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the central laboratory manual.

Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** total bilirubin <2xULN or INR≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** total bilirubin <2xULN or INR≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) until they resolve, stabilise or return to within baseline. • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, (total bilirubin <2xULN and INR ≤1.5) continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and total bilirubin <2xULN and INR ≤1.5, monitor participants twice monthly until liver chemistries resolve or return to within baseline.

References

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

10.7. Appendix 7: AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the Sponsor will comply with all local medical device reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.1.1 for the list of GSK medical devices).

10.7.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• An AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. • An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term ‘life-threatening' in the definition of ‘serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

• A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalisation. Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to foetal distress, foetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.7.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

10.7.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- Other measures to evaluate AEs and SAEs may be utilised (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/device deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.7.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor or the SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool

- Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the Medical Monitor or the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

10.7.6. Reporting of SADEs

SADE Reporting to GSK

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

10.8. Appendix 8: Anaphylaxis Criteria

Joint National Institute of Allergy and Infectious Disease (NIAID)/ Food Allergy and Anaphylaxis Network (FAAN) Second Symposium on Anaphylaxis [Sampson, 2006]. The criteria do not make a distinction based on underlying mechanism. These criteria are summarised as follows:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalised hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
    a) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a) Involvement of the skin-mucosal tissue (e.g., generalised hives, itch-flush, swollen lips-tongue-uvula)
    b) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a) Adolescents (aged 12-17): low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

10.9. Appendix 9: Daily Asthma Symptom Score

Each morning, participants will record an asthma symptom score using the following scale:

Daily Symptom Score:

- 0 = No symptoms during the previous 24-hours.
- 1 = Symptoms for one short period during the previous 24-hours.
- 2 = Symptoms for two or more short periods during the previous 24-hours.
- 3 = Symptoms for most of the previous 24-hours which did not affect my normal daily activities.
- 4 = Symptoms for most of the previous 24-hours which did affect my normal daily activities.
- 5 = Symptoms so severe that I could not go to work/school or perform normal daily activities.

10.10. Appendix 10: Low, Medium and High Daily Doses of Inhaled Corticosteroids

Daily medium and high dose ICS options for adults and adolescents (12 years and older) are shown in Figure 1.

Figure 1 Low, medium and high daily doses of inhaled corticosteroids

Box 3-6. Low, medium and high daily doses of inhaled corticosteroids

This is not a table of equivalence, but instead, suggested total daily doses for the 'low', 'medium' and 'high' dose ICS options for adults/adolescents, p.54 and children 6–11 years, p.55, based on available studies and product information. Data on comparative potency are not readily available and therefore this table does NOT imply potency equivalence. Doses may be country-specific depending on local availability, regulatory labelling and clinical guidelines.

Low dose ICS provides most of the clinical benefit of ICS for most patients with asthma. However, ICS responsiveness varies between patients, so some patients may need **medium dose ICS** if their asthma is uncontrolled despite good adherence and correct technique with low dose ICS (with or without LABA). **High dose ICS** (in combination with LABA or separately) is needed by very few patients, and its long-term use is associated with an increased risk of local and systemic side-effects, which must be balanced against the potential benefits.

Inhaled corticosteroid	Total daily ICS dose (mcg) – see notes above		
	Low	Medium	High
Adults and adolescents (12 years and older)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (pMDI, extrafine particle*, HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle*, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	200		400
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400
Children 6–11 years – see notes above (for children 5 years and younger, see Box 6-6, p.153)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle*, HFA)	50-100	>100-200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80-160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50-100	>100-200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50-100	>100-200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; n.a. not applicable; pMDI: pressurized metered dose inhaler (non-chlorofluorocarbon formulations); ICS by pMDI should preferably be used with a spacer. *See product information.

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10.11. Appendix 11: Recommended Measures Related to COVID-19 Pandemic

Overall Rationale for this Appendix:

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the study intervention or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the study intervention or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

STUDY PROCEDURES DURING COVID-19 PANDEMIC

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrolment and treatment decisions for trial participants.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants.

- Clinical investigators should document in site files and in participant notes/Electronic Heath Records as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).

- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

- Spirometry should not be conducted for participants with confirmed/suspected COVID-19.

Protocol Defined Procedures/Visits:

- Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, measurement of vital signs and weight, and preparation

and administration of study drug (at the discretion of the investigator). It is the responsibility of the investigator to inform GSK when this occurs and to document in source notes.

- Remote visits may be performed at the participant's home by qualified study personnel or at a local medical facility, unless the investigator deems that a site visit is necessary.
- Additional unscheduled safety assessments such as routine blood sampling may be performed at the discretion of the investigator including in the participant's home, if deemed necessary. Biological samples may be collected at a different location, other than the study site (e.g., at participant's home) by qualified study personnel or at a local medical facility according to standard operating procedures and applicable regulations (see note). Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If visits to a site/home are not feasible, then the medical evaluation of the participant's asthma may take place by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress. GSK will be accountable for working with the vendor to ensure the site has the required equipment, training and support for this model and should be notified as soon as possible by the investigator that the service is required.
- The study investigator is responsible for ensuring that the identification, management, and reporting of AEs and SAEs are completed in accordance with the protocol and applicable regulations. AEs are first reported by participants to the investigator/study team or may be identified by the study team during interactions with the participants via telemedicine encounters. In addition, mobile nurses may identify AEs as well and report them to the investigator for evaluation. Additionally, AEs may be identified from lab reports, imaging or ECG reports, and other records. As determined by the investigator, the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary.
- The participant should be informed of the plan and any potential risks associated with the virtual medium and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.
- The revised schedule of study activities is provided in Table 6.

Note: If the investigator wishes to conduct a trial visit at a location that has not been previously assessed by GSK, it is the investigator's responsibility to identify an adequate alternate location and to notify GSK of the alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, is well-equipped to perform study procedures and covered by an adequate insurance. Furthermore, the investigator should have sufficient oversight to ensure that the staff at the alternate location are trained to perform study procedures. Refer to and follow most recent local guidance and regulations if available or refer to FDA or EMA guidance available at time.

Study Intervention:

- If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (see Section 6 Study Intervention and Concomitant Therapy), a maximum dose interval of 28 weeks may be used.
- In-clinic visits are required for administration of the study intervention (Week 0 and Week 26).
- In some cases, trial participants who no longer have access to study intervention or the investigational site may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment).

Data Management/Monitoring:

- The medical problems and healthcare utilisation worksheet may be transmitted from and to the investigator by electronic mail and or conventional mail. If copies/scans of the paper worksheet are sent to the investigator by electronic mail, the participant should be instructed to maintain the original documents and to return them to the site when a visit to the site will be allowed.
- If the eDiary device was provided to the participant, it may be returned to the site by conventional mail after the end of the relevant data collection period (Visit 17 Exit Visit).
- If on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a patient and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.
- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilised during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK.

Assessments that can be Conducted Outside Clinical Study Site:

Activities/assessments that may be conducted outside of a clinical study site are indicated in Table 6.

- White boxes represent activities/assessments that are to be done during visits to the clinical study centre (pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 10, Exit Visit 17, and WS Visit if applicable).
- Grey boxes represent activities/assessments during study visits (Visits 3-9, Visits 11-16, and the FU Visit) that may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow (at the discretion of the investigator, based on safety and tolerability).
- The FU Visit may be conducted as a remote/home visit or as a phone call.
- During home visits, the scheduled collection of samples for laboratory and other assessments may be performed by a home healthcare professional.

Table 6 Schedule of Activities (SoA) Indicating Assessments that may be Conducted Outside of a Clinical Study Site

Protocol Activity	Pre-Screening	Screening /Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
General Eligibility Assessments																					
Informed consent [a]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote a.
Genetic sample informed consent [d]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote d.
Demography and childbearing status	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; All females must be assessed at Visit 1 to determine childbearing potential.
Inclusion/Exclusion criteria	X	X																			
Historical blood eosinophil count		X																			See footnote e.
Medical history		X																			Include cardiovascular (CV), CV risk factors, asthma, exacerbations, vasculitis, allergies and anaphylaxis.
Smoking status		X																			
Parasite screening		X																			Only required in regions with high-risk or for participants who have visited a high-risk region in the past 6 months. Use local laboratories for this test.
eDiary registration and training		X																			Conduct thorough eDiary training at Screening Visit 1 and throughout the study on as-needed basis.
Randomisation criteria			X																		Assess prior to randomisation; see footnote e.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Efficacy Assessments																					
Review for exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spirometry (pre- and post-bronchodilator FEV_1)		X	X								X							X	X		FEV_1=Forced expiratory volume in 1 second; Spirometry should not be conducted for participants with confirmed/suspected COVID-19 (see Section 8.2.3).
ACQ-5			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		ACQ-5=Asthma Control Questionnaire-5
Review eDiary (asthma symptoms, PEF summary)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PEF=Peak expiratory flow
HRQoL: PRO and Health Outcomes Assessments																					
SGRQ			X		X		X				X				X			X	X		SGRQ=St. George's Respiratory Questionnaire
PROMIS (fatigue items)			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PROMIS= Patient-reported outcomes measurement information system
SNOT-22			X								X							X	X		SNOT-22=Sino-nasal Outcomes Test-22 Questionnaire
Complete ADSD/ANSD		←========= daily =========→							X	X	X	X	X	X	X	X	X	X			ADSD/ANSD=Asthma Daily/Nightly Symptom Diary; To be completed daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.
Clinician-rated response to therapy							X				X				X			X	X		
Patient-rated response to therapy							X				X				X			X	X		

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0** [a]	**Visit 1** [a]	**V2**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
PGI-S		X	X				X		X		X				X			X	X		PGI-S: Patient Global Impression of Severity (of asthma)
PGI-C							X		X		X				X			X	X		PGI-C: Patient Global Impression of Change (from baseline of asthma severity)
Safety Assessments																					
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Ensure maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications are reviewed.
Physical Examination		X																X	X		Include height and weight for the complete physical exam at Screening Visit 1. Height can be omitted for subsequent visits.
Vital Signs		X	X			X			X		X	X			X		X	X	X		
12-lead ECG		X	X								X							X	X		
AE/SAE Assessment	X [g]	X [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE=Adverse events; SAE=Serious adverse events; see footnote g.
Laboratory Assessments																					
Haematology with differential [f]		X [e]	X	X	X	X	X		X		X	X	X		X		X	X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing; see footnotes e and f.
Total IgE			X																		
Clinical Chemistry		X	X		X	X	X		X		X	X			X			X	X		Include liver chemistry.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Pregnancy Test (WOCBP only)		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	Serum pregnancy test should be done at screening Visit 1 and Exit Visit; urine pregnancy tests should be done for all other assessments; WOCBP=Women of childbearing potential; See Section 8.3.5 for additional information.
Urinalysis		X	(X)								X							X	X		Conduct at Visit 2 if not completed at Visit 1. Note: dipstick, send for analysis if abnormality is identified by dipstick
Anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			X																		ANA=antinuclear antibodies; MPO=myeloperoxidase; PR3=proteinase 3. Collected baseline sample will be stored and may be tested if necessary (see Section 7.5).
Complement C3 and C4			X				X				X				X			X	X		
PK sample			X	X	X	X	X		X		X	X	X		X			X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing.
Immunogenicity sample			X	X	X	X	X				X	X	X	X	X			X	X		
Blood biomarker sample			X				X				X				X			X			Sample will be stored and may be analysed for exploratory biomarkers (see Section 8.7.3) **China only:** Blood samples for exploratory biomarkers will not be collected from participants in China.
Genetics sample			←==========					The genetics sample can be collected at Visit 2 or any visit after									==========→				See footnote d.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Study intervention																					
Administer study intervention			X								X										Study intervention will only be administered in the clinic. Any scheduled assessments or sample draws should be performed beforehand. Monitor participant for at least 2h after administration (see Section 6.5).
eCRF/worksheets/other																					
Dispense Rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Register Visit in the IRT system	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	IRT=interactive response technology
Provide worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				The worksheet is a medical problems and healthcare utilisation worksheet.
Review worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
eDiary close out																		X	X		
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		eCRF=electronic Case Report Form

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	

a. Informed Consent must be obtained prior to initiating any study assessments. Pre-screening Visit 0 can occur any time from 0 to 14 days before Screening Visit 1.

b. Randomisation Visit 2 is 1 week after Screening Visit 1 but can be extended to up to 6 weeks after Visit 1 if, for example, a participant has an exacerbation during the run-in period. Results from Screening Visit 1 procedures must be available for review of randomisation criteria.

c. If a participant withdraws from the study, then the Withdraw from Study (WS) Visit should be conducted 26 weeks after the last administered dose of study intervention, i.e., at Week 26 if the second dose of study intervention was not received, or at Week 52 if the second dose of study intervention was received. A follow-up visit/call should also be conducted 30 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing.

d. Informed Consent for optional genetics research must be obtained before collecting a sample. **China only:** Genetic Informed Consent will not be collected from participants in China. Genetic blood samples will not be collected from participants in China.

e. To be randomised, participants without a historical blood eosinophil count of ≥300 cells/µL in the 12 months prior to Screening Visit 1, must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1.

f. For haematology samples collected after Randomisation, the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will not be reported to site staff and Sponsor (to maintain the treatment blind). However, sites will be sent total white blood counts throughout the study. Samples should be taken prior to dosing at Week 0 and Week 26 visits.

g. SAEs must be collected from signing of Informed Consent if considered related to study procedures.

10.12. Appendix 12: Country-specific requirements

Participants in China will not participate in the genetics (Appendix 5) or exploratory biomarker (Section 8.7.3) research.

10.13. Appendix 13: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine transaminase
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibody
ADE	Adverse device events
ADSD	Asthma Daily Symptom Diary
ANSD	Asthma Nightly Symptom Diary
Anti-HBc	Hepatitis B core antibody
Anti-IL-5	Anti-Interleukin-5
Anti-IL-5R	Anti-Interleukin-5 receptor
AST	Aspartate aminotransferase
BiPAP	Bilevel positive airway pressure
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
cm	Centimetre
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous positive airway pressure
CPK	Creatine phosphokinase
CRF	Case report form
CS	Corticosteroid
CSR	Clinical study report
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
ECG	Electrocardiogram
ED	Emergency department
eDiary	Electronic diary
EDTA	Ethylenediaminetetraacetic acid or disodium edetate
EGPA	Eosinophilic granulomatosis with polyangiitis
FAAN	Food Allergy and Anaphylaxis Network
FEV_1	Forced expiratory volume in 1 second
FP	Fluticasone propionate
FSH	Follicle stimulating hormone
FTIH	First Time in Humans
FVC	Forced vital capacity

g	Grams
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma glutamyl transferase
GINA	Global Initiative for Asthma
GLDH	Glutamate dehydrogenase
GSK	GlaxoSmithKline
h	Hours
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HFA	Hydrofluoroalkane product
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IFU	Instruction for use
Ig	Immunoglobulin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IM	Intramuscular
IMP	Investigational medicinal product
INR	International normalised ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
kg	kilogram
L	Litre
LA	Long-acting
LABA	Long-acting β-agonist
LAM	Lactational amenorrhea method
LAMA	Long-acting muscarinic antagonist
LDH	Lactate dehydrogenase
LTRA	Leukotriene receptor antagonist
mAb	Monoclonal antibody
MAR	Missing at random
mcg (μg)	Microgram

MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Millilitres
mm Hg	Millimetre of mercury
mol	Mole
MPO	myeloperoxidase
MSDS	Material Safety Data Sheet
msec	Milliseconds
NAb	Neutralising antibody
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NIMP	Non-investigational medicinal product
OCS	Oral corticosteroid
OLE	Open-label extension
PC_{20}	Provocative concentration causing a 20% fall in FEV_1
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PD_{20}	Provocative dose that decreases FEV_1 by 20%
PEF	Peak expiratory flow
PFS	Pre-filled safety syringe
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PR3	Proteinase 3
PRO	Patient-reported outcomes
PROMIS	Patient-reported outcomes measurement information system
QTcF	QTc corrected by Fridericia's formula
QTL	Quality tolerance limits
R&D	Research and Development
RNA	Ribonucleic acid
RBC	Red blood cell
SABA	Short-acting β-agonist
SADE	Serious adverse device event
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SGPT	Serum glutamic pyruvic transaminase
SGOT	Serum glutamic oxaloacetic transaminase
SGRQ	St. George's Respiratory Questionnaire
SNOT	Sino-nasal Outcomes Test
SoA	Schedule of assessments
SoC	Standard of care

SOC	System organ class
SRM	Study Reference Manual
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
UACR	Urinary albumin-creatinine ratio
UK	United Kingdom
ULN	Upper Limit of Normal
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential
w/v	Weight/volume
µL	Microlitre

Trademark Information

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TITLE PAGE

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Protocol Number: 206713/Amendment 02

Compound Number or Name: GSK3511294

Brief Title: Placebo-controlled efficacy and safety study of GSK3511294 (depemokimab) in participants with severe asthma with an eosinophilic phenotype

Study Phase: Phase 3A

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information can be found in the Study Reference Manual (SRM).

Sponsor Signatory:

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Vice President and Disease Area Lead, Respiratory

Manufacturer: GlaxoSmithKline

Regulatory Agency Identifying Number(s):

IND: 146742

EudraCT: 2020-003632-25

Approval Date: 08 Apr 2022

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Number**
Amendment 02	08 Apr 2022	TMF-14449557
Amendment 01	*17-AUG-2021*	TMF-13331263
Original Protocol	*01-Oct-2020*	TMF-2125331 (2020N439965_00)

Amendment 02: 08 Apr 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Amendment 02 is a global amendment to include details about controlled early access to unblinded pharmacokinetics (PK) and pharmacokinetics pharmacodynamics (PKPD) data, a futility analysis and the use of blinded interim data to complete a psychometric analysis of the Asthma Daily/Nightly Symptom Diary (ADSD/ANSD) and PROMIS fatigue items. Additional changes include repeated spirometry assessment and/or additional lab test if randomisation criteria are not met during screening, change in the ratio of medium/high ICS dose, allowance/permittance of authorized COVID-19 treatments, Global Initiative for Asthma (GINA) inhaled corticosteroid (ICS) doses update, and QT prolongation clarifications. Added note for exclusion of adolescents in Germany, United Kingdom (UK), Russia. Text added related to special procedure for the urinalysis in China sites.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA)	Added new footnote “h” spirometry retest allowed during the run in period if a patient fails the protocol-specified reversibility criterion or FEV_1 inclusion criteria Added text to clarify that pregnancy text should be done at screening Visit 1 and Exit Visit/Withdraw from study visit Updated text in footnote “e” the Screening Visit laboratory assessment can be repeated during the run in period if a patient does not meet the blood	To add flexibility in screening tests; current information suggests this change is expected to result in improved screening while maintaining the integrity of the patient population Clarification To add flexibility in screening tests; current information suggests this change is expected to result in improved screening

Section # and Name	Description of Change	Brief Rationale
	eosinophil count eligibility criteria at the Screening Visit test result Added text to clarify that, electrocardiogram (ECG) must be performed and assessed pre-dose Added text to clarify that 12-lead ECG central over-read values should be used at all visits with the exception of Visit 2 and Visit 10 where 12-lead ECG machine read values should be used	while maintaining the integrity of the patient population Clarification Clarification
Section 1.3 Schedule of Activities SoA (Urinalysis) 10.2 Appendix 2: Clinical Laboratory Tests Section 10.11 Appendix 11: Recommended measures Related to COVID-19 Pandemic (Table 6)	Text added to clarify that for China sites the urine specimen may be sent to the central laboratory for routine urinalysis instead of performing a local urine dipstick. Urinalysis should be performed at Visit 1 so that results are available before randomisation at Visit 2.	Country specific procedure
Section 2.3.1 Risk Assessment (QTc prolongation)	Removed text related to post-baseline QTcF value of potential clinical importance from first time in human (FTIH) study (205722) Updated text related to ECG parameters including corrected QT interval using Fridericia's formula (QTcF) for depemokimab treatment groups in the FTIH study (205722) Updated wordings related to analysis of the relationship between depemokimab plasma concentrations and change from baseline QTcF data collected in FTIH 205722 study	Modified text related to ECG parameters in the FTIH study (205722) for better clarity. No new safety information.

Section # and Name	Description of Change	Brief Rationale
Section 4.1 Overall Design Section 6.4.1 Treatment Assignment	Changed the ratio of medium/high ICS dose from 25% medium ICS dose and 75% high ICS dose to aiming up to 50% approximately of participants on medium ICS dose	To better reflect dosing in clinical practice while maintaining the integrity of the patient population
Section 5.1 Inclusion Criteria	Added note to clarify that, in UK, Russia and Germany only adult participants (≥18 years) are to be included in this clinical trial	Clarification
Section 5.2 Exclusion Criteria (Prior/Concomitant therapy)	Text added in exclusion criteria no. 12 to clarify that Authorized monoclonal antibodies (mAbs) treatments for COVID-19 are permitted	Allowance of treatments for COVID-19 is not expected to impact the overall interpretability of the data generated from this study or lead to any safety concern with concomitant use of IMP
Section 5.2 Exclusion Criteria (Diagnostic Assesments)	Text added in exclusion criteria no.15 to clarify that the 12-lead ECG central over-read QTcF value is to be used	Clarification
Section 5.3.2 Randomisation Exclusion Criteria	Text added in randomisation exclusion criteria no. 3 to clarify that the 12-lead ECG machine read QTcF value is to be used at Visit 2. The central over-read of the Screening Visit 1 12-lead ECG should be used to review ECG findings at Visit 2.	Clarification
Section 6.4.3 Controlled Early Access to Unblinded PK and PKPD Data	Added sub section and included text regarding controlled early access to Unblinded PK and PKPD Data to designated independent representative(s)	Allow for development of PK/PD models and expedited reporting
Section 6.9.1 Permitted Medications and Non-Drug Therapies	"Additional asthma medications such as theophyllines and anti-leukotrienes will be permitted **as maintenance** provided that they have been taken regularly in the 3 months prior to screening (Visit 1)".	Clarification Repeated text removed

Section # and Name	Description of Change	Brief Rationale
	Removed repeated wordings about vaccination against SARS-CoV-2 infection using authorized COVID-19 vaccines Text added to clarify that participants can be treated for SARS-CoV-2 infection using authorized COVID-19 treatments (including mAbs) in line with local/national guidelines. Experimental COVID-19 treatments are not permitted	Allowance of treatments for COVID-19 is not expected to impact the overall interpretability of the data generated from this study or lead to any safety concern with concomitant use of IMP
Section 7.1.2 QTc Stopping Criteria	Text added to clarify that the QTcF value from the 12-lead ECG central over-read at randomisation Visit 2 should be used as baseline QTcF value for any changes from baseline calculations during the study Text added to clarify that after randomisation 12-lead ECG central over-read values should be used to assess QTc stopping criteria, with the exception of Visit 10 (Week 26) where 12-lead ECG machine read values should be used	Clarification Clarification
Section 8.1.2 Critical Assessment performed at Screening (Visit 1)	Added new text to clarify that if the Screening Visit test result does not meet the blood eosinophil count eligibility criteria, the laboratory assessment may be repeated, at the discretion of the investigator Added text for spirometry to clarify that if a patient fails the protocol-specified reversibility criterion or FEV1 inclusion criteria, spirometry restest is allowed during the run-in period	To add flexibility in screening tests; current information suggests this change is expected to result in improved screening while maintaining the integrity of the patient population To add flexibility in screening tests; current information suggests this change is expected to result in improved screening while maintaining the integrity of the patient population

Section # and Name	Description of Change	Brief Rationale
Section 8.3.3 Electrocardiograms (ECGs)	Updated text related to additional ECGs to be performed if an ECG demonstrates a prolonged QTcF interval	Revised wording for clarification
Section 9.2.1 Sample Size Assumptions	Added text regarding the possibility that greater than 375 participants will be randomised in the study due to local country requests or requirements	Clarification
Section 9.2.3 Sample Size Re-estimation or Adjustment	Text related to the data to be used for clinical study report has been deleted.	All data (pre and post- target enrolment) would be used for clinical study report
Section 9.3 Analysis Sets	Updated text related to screened, enrolled, randomised, full analysis set, and safety population	Revised description of Analysis sets
Section 9.4.5 Safety Analyses	Safety population used for Safety analyses instead of mITT	To provide clarification that all safety analyses will be performed on the Safety Population
Section 9.6 Interim Analysis	Text deleted “no interim analyses are planned” Added text that an unblinded interim analysis for futility will be performed Added text to describe that blinded interim data will be used to complete a psychometric analysis of the ADSD/ANSD and PROMIS fatigue items	Text removed to align with new interim analysis Futility analysis conducted to further evaluate benefit/risk As part of the validation of the ADSD/ANSD and PROMIS fatigue items a blinded, data cut off will be used to complete a psychometric analysis of the measures
10.7.4 Recording and Follow-up of AE and/or SAE and Device Deficiencies (Assessment of Intensity)	Text deleted “other measures to evaluate AEs and SAEs may be utilised”.	Clarification
Appendix 10 Medium and High Daily Doses of Inhaled Corticosteroids	Footnote added to clarify GINA 2021 guidelines updates	Update as per GINA 2021 guidelines
Section 11 References	Added and updated the reference	Updated the references
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Brief Title: Placebo-controlled efficacy and safety study of GSK3511294 (depemokimab) in participants with severe asthma with an eosinophilic phenotype

Rationale:

GSK3511294 is being developed as a long-acting (LA) subcutaneous (SC) injectable anti-interleukin-5 (anti-IL-5) therapy and is expected to deliver an efficacy and safety profile similar to current anti-IL-5 therapies with a reduced dosing frequency (once every 26 weeks). The aim of this study is to investigate the efficacy and safety, over a 52-week treatment period, of GSK3511294 100 mg SC given once every 26 weeks as adjunctive therapy in participants with uncontrolled severe asthma with an eosinophilic phenotype.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

Overall Design:

This study employs a multi-centre, randomised, placebo-controlled, double-blind, parallel group design to assess the efficacy and safety of GSK3511294 in participants with severe uncontrolled asthma with an eosinophilic phenotype despite standard of care (SoC) treatment with medium to high dose inhaled corticosteroid (ICS) plus at least one additional controller. All participants will receive study intervention as an adjunct therapy while remaining on their existing asthma therapy throughout the study.

Brief Summary:

The purpose of this study is to assess the efficacy and safety of GSK3511294 as an adjunctive therapy in participants with severe uncontrolled asthma with an eosinophilic phenotype. During the 52-week treatment period, participants will receive two doses (at Week 0 and Week 26) of add-on study intervention (GSK3511294 100 mg or matching placebo) by SC injection, while remaining on their existing maintenance asthma therapy (that excludes biologics) throughout the study. Assessments will include the annualised rate of clinically significant exacerbations and measures of lung function, asthma control, and safety.

Number of Participants:

Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125).

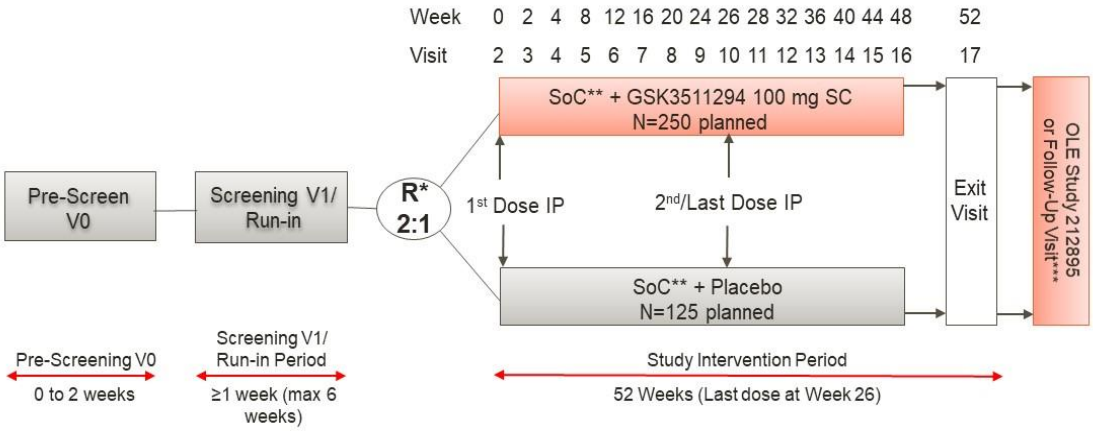
Intervention Groups and Duration:

The study will consist of a pre-screen period (0-2 weeks), a run-in period (1-6 weeks), and a study intervention period (52 weeks). After the run-in period, participants will be randomised in a 2:1 ratio using an interactive response technology (IRT) system in a blinded manner to receive either GSK3511294 100 mg or placebo by SC injection. Randomisation will be stratified based on baseline ICS dose (medium or high dose). Two doses of study intervention will be administered in the clinic: the first at randomisation Visit 2 (Week 0) and the second at Visit 10 (Week 26). Participants will be assessed at each scheduled visit (a total of 17 study visits) during the 52-week treatment phase. Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 3, Visit 10, Visit 11 Exit Visit 17, and WS Visit (if applicable).

Participants who receive both doses of study intervention and complete the Exit Visit will be eligible to participate in an open-label extension (OLE) study (Study 212895), during which they will receive two doses of open-label GSK3511294 100 mg SC over another 52 weeks. Participants who do not enter the OLE study will have a follow-up visit/call at Week 56.

Independent Data Monitoring Committee: Yes

1.2. Schema



** R = Randomisation: To be randomised participants without a historical blood eosinophil count of ≥300 cells/µL must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. Participants will remain on their standard of care (SoC) asthma therapy throughout the intervention period and will be randomised 2:1 to receive GSK3511294 (100 mg) or placebo.*
*** SoC = medium to high dose ICS (≥440 µg FP HFA daily or clinical comparability) plus additional controller. SoC asthma therapy to exclude biologics.*
**** OLE = Open label extension. Willing participants will continue directly into OLE Study 212895. Participants unwilling to continue will have a follow-up visit 4 weeks after the Exit Visit.*

1.3. Schedule of Activities (SoA)

Protocol Activity	Pre-Screening	Screening/Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	**V0** [a]	**Visit 1** [a]	**V2**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
General Eligibility Assessments																					
Informed consent [a]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote a.
Genetic sample informed consent [d]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote d.
Demography data collection	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; All females must be assessed at Visit 1 to determine childbearing potential.
Inclusion/Exclusion criteria	X	X																			
Historical blood eosinophil count		X																			See footnote e.
Medical history		X																			Include cardiovascular (CV), CV risk factors, asthma, exacerbations, vasculitis, allergies and anaphylaxis.
Smoking status		X																			

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Parasite screening		X															X				Only required in regions with high-risk or for participants who have visited a high-risk region in the past 6 months. Use local laboratories for this test. For details refer to study reference manual (SRM).
eDiary registration and training		X																			Conduct thorough eDiary training at Screening Visit 1 and throughout the study on as-needed basis.
Randomisation criteria			X																		Assess prior to randomisation; see footnote e.
Efficacy Assessments																					
Review for exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Collection of exacerbations at Visit 1 is historical data.
Spirometry (pre- and post-bronchodilator FEV_1)[h]		X	X								X							X	X		FEV_1=Forced expiratory volume in 1 second; Spirometry should not be conducted for participants with confirmed/suspected COVID-19 (see Section 8.2.3).
ACQ-5			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		ACQ-5=Asthma Control Questionnaire-5

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Review eDiary (asthma symptoms, PEF summary)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PEF=Peak expiratory flow
HRQoL: PRO and Health Outcomes Assessments																					
SGRQ			X		X		X				X				X			X	X		SGRQ=St. George's Respiratory Questionnaire
PROMIS (fatigue items)			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PROMIS= Patient-reported outcomes measurement information system
SNOT-22			X								X							X	X		SNOT-22=Sino-nasal Outcomes Test-22 Questionnaire
Complete ADSD/ANSD		←========= daily =========→							X	X	X	X	X	X	X	X	X	X			ADSD/ANSD=Asthma Daily/Nightly Symptom Diary; To be completed daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.
Clinician-rated response to therapy							X				X				X			X	X		

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0** [a]	**Visit 1** [a]	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Patient-rated response to therapy							X				X				X			X	X		
PGI-S		X	X				X		X		X				X			X	X		PGI-S: Patient Global Impression of Severity (of asthma)
PGI-C							X		X		X				X			X	X		PGI-C: Patient Global Impression of Change (from baseline of asthma severity)
Safety Assessments																					
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Ensure maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications are reviewed.
Physical Examination		X																X	X		Include height and weight for the complete physical exam at Screening Visit 1. Height can be omitted for subsequent visits.
Vital Signs		X	X			X			X		X	X			X		X	X	X		

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
12-lead ECG		X	X	X							X	X						X	X		ECG must be performed and assessed pre-dose. Twelve-lead ECG central over-read values should be used at all visits with the exception of Visit 2 and Visit 10 where 12-lead ECG machine read values should be used.
AE/SAE Assessment	X [g]	X [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE=Adverse events; SAE=Serious adverse events; see footnote g.
Laboratory Assessments																					
Haematology with white blood cells count [f]		X [e]	X	X	X	X	X		X		X	X	X		X		X	X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing; see footnotes e and f.
Total IgE			X																		
Clinical Chemistry		X	X		X	X	X		X		X	X			X		X	X	X		Include liver chemistry.
Pregnancy Test (WOCBP only)		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	Serum pregnancy test should be done at screening Visit 1 and Exit Visit/ Withdraw from study visit; urine pregnancy tests should be done for all other assessments; WOCBP=Women of childbearing potential; See Section 8.3.5 for additional information.

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Urinalysis		X	(X)								X							X	X		Conduct at Visit 2 if not completed at Visit 1. Note: dipstick, send for analysis if abnormality is identified by dipstick **China Only:** For China sites the urine specimen may be sent to the central laboratory for routine urinalysis instead of performing a local urine dipstick. Urinalysis should be performed at Visit 1 so that results are available before randomisation at Visit 2. Urine pregnancy test must still be performed at the site.
Anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			X																		ANA=antinuclear antibodies; MPO=myeloperoxidase; PR3=proteinase 3. Collected baseline sample will be stored and may be tested if necessary (see Section 7.5).
Complement C3 and C4			X				X				X				X			X	X		
PK sample			X	X	X	X	X		X		X	X	X		X			X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing.

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Immunogenicity sample			X	X	X	X	X				X	X	X	X	X			X	X		
Blood biomarker sample			X				X				X				X			X			Sample will be stored and may be analysed for exploratory biomarkers (see Section 8.7.3) **China only:** Blood samples for exploratory biomarkers will not be collected from participants in China.
Genetics sample			←========== The genetics sample can be collected at Visit 2 or any visit after ==========→																		See footnote d.
Study intervention																					
Administer study intervention			X								X										Study intervention will only be administered in the clinic. Any scheduled assessments or sample draws should be performed beforehand. Monitor participant for at least 2h after administration (see Section 6.5).
eCRF/worksheets/other																					
Dispense Rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Register Visit in the IRT system		X	X								X								X		IRT=interactive response technology
Provide worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				The worksheet is a medical problems and healthcare utilisation worksheet.
Review worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
eDiary close out																		X	X		
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		eCRF=electronic Case Report Form

a. Informed Consent must be obtained prior to initiating any study assessments. Pre-screening Visit 0 can occur any time from 0 to 14 days before Screening Visit 1.

b. Randomisation Visit 2 is 1 week after Screening Visit 1 but can be extended to up to 6 weeks after Visit 1 if, for example, a participant has an exacerbation during the run-in period. Results from Screening Visit 1 procedures must be available for review of randomisation criteria.

c. If a participant withdraws from the study, then the Withdraw from Study (WS) Visit should be conducted 26 weeks after the last administered dose of study intervention, i.e., at Week 26 if the second dose of study intervention was not received, or at Week 52 if the second dose of study intervention was received. A follow-up visit/call should also be conducted 30 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing.

d. Informed Consent for optional genetics research must be obtained before collecting a sample. **China only:** Genetic Informed Consent will not be collected from participants in China. Genetic blood samples will not be collected from participants in China.

e. To be randomised, participants without a historical blood eosinophil count of ≥300 cells/µL in the 12 months prior to Screening Visit 1, must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. If the Screening Visit test result does not meet the blood eosinophil count eligibility criteria, the laboratory assessment may be repeated, at the discretion of the investigator, if it is judged to be likely in the eligible range for study inclusion within the run-in period prior to Visit 2.

f. For haematology samples collected after Randomisation, the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will not be reported to site staff and Sponsor (to maintain the treatment blind). However, sites will be sent total white blood counts throughout the study. Samples should be taken prior to dosing at Week 0 and Week 26 visits.

g. SAEs must be collected from signing of Informed Consent if considered related to study procedures
h. If a patient fails the protocol-specified reversibility criterion or FEV_1 inclusion criteria, spirometry retest is allowed during the run-in period.

2. INTRODUCTION

2.1. Study Rationale

Anti-IL-5 therapies have an established efficacy and long-term safety profile and are a cornerstone of severe asthma management for patients with an eosinophilic phenotype [GINA, 2020]. Three antagonists of IL-5 (mepolizumab and reslizumab) or its receptor (IL-5R) (benralizumab) are approved for severe asthma with an eosinophilic phenotype, as an add-on treatment administered every 4 to 8 weeks.

GSK3511294 (depemokimab) is being developed as a LA SC injectable anti-IL-5 therapy and is anticipated to deliver an efficacy and safety profile similar to current anti-IL-5 therapies with a reduced dosing frequency (once every 26 weeks). The aim of this study is to investigate the efficacy and safety, over a 52-week treatment period, of GSK3511294 100 mg SC given once every 26 weeks as adjunctive therapy to participants with uncontrolled severe asthma with an eosinophilic phenotype.

2.2. Background

Persistent eosinophil inflammation is a feature of more than 50% of patients with severe asthma [Chung, 2014]. Several monoclonal antibodies (mAbs) targeting eosinophil inflammation have received marketing authorisation for asthma with an eosinophilic phenotype, including 3 targeting either interleukin-5 (IL-5) or its receptor (IL-5R): mepolizumab (Nucala), reslizumab (Cinqair/Cinqaero), and benralizumab (Fasenra). All three, by utilising blood eosinophils as a biomarker to predict patients likely to respond to therapy, have been shown to reduce asthma exacerbations, and improve lung function and health-related quality of life (HRQoL), in patients with asthma with an eosinophilic phenotype [Haldar, 2009; Castro, 2011; Pavord, 2012; Bel, 2014; Ortega, 2014; Castro, 2015; Bleecker, 2016; FitzGerald, 2016; Chupp, 2017].

Evidence supporting the tolerability of targeting IL-5/5R is provided by long-term extension studies for mepolizumab [Lugogo, 2016; Khatri, 2019; Khurana, 2019], reslizumab [Murphy, 2017], and benralizumab [Busse, 2019] as well as efficacy data in real-world evidence settings for mepolizumab [Harrison, 2020; Bagnasco, 2019; Pertzov, 2019; Schleich, 2020]. Clinical trial data over more than 10 years combined with real-world evidence, have demonstrated that treatments targeting the IL-5 pathway are both highly effective and well-tolerated. Based on this established efficacy and safety, anti-IL-5/5R therapies are now a cornerstone of severe asthma management and are endorsed by international guidelines for appropriate patients that continue to exacerbate despite optimised care with Step 4 or Step 5 treatment (medium and high dose ICS) [GINA, 2020].

GSK3511294 is a humanised, affinity matured mAb that blocks human IL-5 binding to its receptor and belongs to the established class of anti-IL-5 therapies for severe asthma management. Compared with mepolizumab, GSK3511294 contains 7 amino acid substitutions to the heavy chain sequence: 4 amino acid changes introduced in the heavy chain variable region and 3 amino acid changes (YTE) in the Fc region. The resulting antibody has increased affinity and half-life. Evidence to date indicate that these amino acid changes extend the pharmacokinetics (PK) and pharmacology of GSK3511294 to

enable less frequent dosing with an anticipated similar efficacy and safety profile relative to mepolizumab (administered chronically).

Long-acting alternatives that can be administered on a less frequent basis are recognised as successful approaches for chronic indications. As a LA anti-IL-5 therapy, GSK3511294 is anticipated to have an efficacy and safety profile that is similar to those of the currently-approved therapies in its class, but with a single administration every 26 weeks, as opposed to the current regimen of every 4 weeks for mepolizumab and reslizumab, or every 8 weeks for benralizumab (every 4 weeks for the first 3 doses).

A detailed description of the chemistry, pharmacology, and safety of GSK3511294 is provided in the current Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2016N295843_03 or later].

2.3. Benefit: Risk Assessment

Summaries of findings from non-clinical studies conducted with GSK3511294 and completed FTIH study 205722 can be found in the current IB [GlaxoSmithKline Document Number 2016N295843_03 or later]. The following section outlines the risk assessment and mitigation strategy for this protocol:

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention GSK3511294		
• Allergic reactions including anaphylaxis.	• Allergic reactions with the most severe form being anaphylaxis (see Appendix 8), are potential risks associated with mAbs. • No allergic reactions or anaphylaxis have been reported with GSK3511294 in FTIH study 205722 in participants with mild to moderate asthma. One participant reported an event under Hypersensitivity SMQ with preferred term of rash verbatim "localised rash both bends of arms", 82 days post 30 mg SC dose of GSK3511294. The event was non-serious, of mild intensity, resolved within 10 days and was considered unrelated to the study intervention by the investigator.	• Daily monitoring of serious adverse events (SAEs) by Medical Monitor/SAE coordinator; regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GSK safety review team. • Use of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 8). • Participants will be monitored in clinic for immediate hypersensitivity and any other untoward effects for a minimum of 2 hours post-injection (both at randomisation and at Week 26). In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study intervention, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care if appropriate. • An independent data monitoring committee (IDMC) will review unblinded safety data at regular intervals.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Participants with severe allergic reaction/anaphylaxis with no alternative explanation after the first dose will not receive another dose.
• Type III Hypersensitivity (Immune complex disease/vasculitis)	• Adverse effects of vascular inflammation consistent with immune complex disease were observed in 1 female monkey in the 1-month toxicity study after administration of 10 mg/kg. A further monkey had a minimal focal inflammation after administration of 100 mg/kg. Immune complex disease was not observed in the 6-month repeat dose (2 doses) study at the same doses. It is unknown if this will translate to humans as preclinical models are not necessarily predictive of clinical findings in humans. • No AEs of Type III hypersensitivity have been reported with GSK3511294 in FTIH study 205722 in participants with mild to moderate asthma (36 participants received GSK3511294; 12 participants received placebo).	• Participants with current diagnosis of vasculitis will be excluded. Participants with high clinical suspicion of vasculitis at screening will be evaluated and excluded from enrolment if diagnosed (Section 5.2). • Daily monitoring of SAEs will be done by Medical Monitor/SAE coordinator; regular systematic review of adverse event (AE)/SAE data from ongoing studies will be performed by a GSK safety review team. • IDMC will review unblinded safety data at regular intervals; any events suggestive of immune complex disease will be reviewed by a rheumatologist (member of the IDMC). • Protocol guidance on early identification of vasculitis events is provided (see Section 7.5). • Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation after the first dose will not receive another dose of study intervention (see Section 7.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• Immunogenicity, anti-drug antibodies (ADAs)	• Biopharmaceutical products may elicit ADAs and neutralising antibodies (NAb), which have the potential to modulate PK or pharmacodynamics (PD), or to produce adverse reactions. • In FTIH study 205722, none of the participants tested positive for ADA at baseline. Overall, 9 participants (25%) had confirmed positive results for ADA at any time post-baseline, primarily in the GSK3511294 30 mg dose group (5 participants), which was also the group with the highest total serum IL-5 concentrations. This apparent correlation warrants further investigation. There were no major differences observed in the GSK3511294 plasma concentration profiles and blood eosinophil count-time profiles as well as AE reporting between ADA-positive and ADA-negative participants. Neutralising antibodies were not tested in this study.	• Blood samples will be collected for detection of both ADA and NAb (see Section 8.8).
• Local injection site reactions	• A potential risk of any drug delivered via injection. • No injection site reactions were noted in the preclinical studies. • In the GSK3511294 FTIH study 205722, injection site reactions were reported by one (3%) participant who received	• Daily monitoring of SAEs by Medical Monitor/SAE coordinator; regular systematic review of AE/SAE data from ongoing studies by GSK study team and/or GSK safety review team. • The IDMC will review unblinded safety data at regular intervals.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	GSK3511294 and one (8%) participant who received placebo.	
• QTc prolongation	• Four monkeys in the 6-month repeat dose monkey study administered 100 mg/kg every 3 months (2 doses) were observed to have QTc prolongation (mean change of 18 msec relative to vehicle control value) during Week 14. • In the GSK3511294 FTIH study (205722), no treatment effect for ECG parameters including corrected QT interval (QTcF) was observed across the GSK3511294 treatment groups (n=36). No participants met QTcF protocol specified criteria (QTcF >500 msec or increase from baseline >60 msec, or uncorrected QT >600 msec) that would require additional monitoring. • Analysis of the relationship between GSK3511294 plasma concentrations and change from baseline QTcF data collected in FTIH 205722 study did not reveal any clinically or statistically significant trends of concern with increasing GSK3511294 dose up to 300 mg. The predicted increase in mean QTcF change from baseline with GSK3511294 plasma concentrations point estimates remained below 10 msec [FDA, 2005] up to concentrations of 100 ug/mL, with a 95% lower CI consistent with zero change from baseline (i.e. the 95% lower	• ECGs will be performed according to timepoints specified in the SoA (Section 1.3) and the assessment will be done as specified in Section 8.3.3. • Participants with QTc prolongation on screening will be excluded (criterion 15, Section 5.2). • Participants with a pre-existing clinically significant cardiac medical condition are excluded (criterion 7, Section 5.2). • Participants who meet QT stopping criteria as specified in Section 7.1.2 will not receive another dose of study intervention. • The IDMC will review unblinded safety data at regular intervals.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	bound of the CI is below zero) [GSK Document Number: 2020N457410_00].	
• Risk of GSK3511294 affecting an unborn baby.	• Reproductive studies have not been conducted with GSK3511294; however, in the 6-month repeat dose monkey study no changes were observed in reproductive organs. Seminiferous tubules were evaluated with respect to their stage in the spermatogenic cycle and the integrity of the various cell types present within the different stages in sexually mature males. No cell or stage specific abnormalities were noted. • In addition, there is a low reproductive risk associated with the IL-5 target mechanism (as shown in pre-clinical reproductive toxicology studies of mepolizumab and reslizumab), a low genotoxic concern for mAbs in general, and a low transfer of mAbs into semen due to the inability of large molecular weight proteins such as GSK3511294 to access pivotal cells in the testes [Setchell, 1975; Pollanen, 1995; Pollanen, 1989; Setchell, 2001; Sohn, 2016], the risk of adverse effects on spermatogenesis is considered minimal. Therefore, male participants are not required to use contraception.	• Participants who are pregnant, breastfeeding, or plan to become pregnant at Screening are excluded (criterion 19, Section 5.2). Participants who become pregnant during the study will not receive another dose of study intervention (see Section 7.1). • All female participants will be assessed at screening to determine childbearing status. Female participants of childbearing potential must be using a highly effective contraceptive method from at least 14 days prior to first dose and until 30 weeks after the last administered dose as described in Section 10.4.2.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
• Potential risk for injury with phlebotomy.	• Risks with phlebotomy include bruising, bleeding, infection, nerve damage.	• Procedures to be performed by trained personnel (i.e., study nurse).

2.3.2. Benefit Assessment

Current clinical data from approved anti-IL-5/5R mAbs (mepolizumab, reslizumab, and benralizumab) demonstrate clinical utility in the treatment of conditions associated with elevated eosinophil levels, such as severe asthma with an eosinophilic phenotype. Mepolizumab 100 mg SC (every 4 weeks) is approved as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype. The safety profile of mepolizumab is favourable.

As a LA anti-IL-5 mAb, GSK3511294 is anticipated to provide the same clinical benefit with a similar safety profile compared with mepolizumab and others in its class and with the added benefit of an extended duration of action requiring less frequent SC dosing (once every 6 months). As such, GSK3511294 may offer the convenience of an improved dosing schedule.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures being implemented to minimise risk to participants in this study, the potential risks of participating in this study are justified by the anticipated benefits that may be afforded to participants with severe uncontrolled asthma with an eosinophilic phenotype; therefore, the Sponsor considers that the investigation of the efficacy, and safety of GSK3511294 is justified in this study with a positive benefit: risk ratio.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks
Other	
• To investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	• Time to first clinically significant exacerbation[a] • Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit • Change from baseline in SGRQ total score at discrete timepoints during the 52-week period • Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period • SGRQ total score responder status at Week 52 (responder defined as achieving ≥4-point reduction from baseline) • ACQ-5 score responder status at Week 52 (responder defined as achieving ≥0.5-point reduction from baseline) • Change from baseline in Patient-Reported Outcomes Measurement Information Systems (PROMIS) Fatigue items score at

Objectives	Endpoints
	discrete timepoints during the 52-week period • Change from baseline in Asthma Daily Symptom Diary (ADSD)/ Asthma Nightly Symptom Diary (ANSD) weekly mean score at specified timepoints during the 52-week period • Change from baseline in awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean • Change from baseline in morning peak expiratory flow (PEF) 2-week mean • Change from baseline in daily asthma symptom scores 2-week mean • Change from baseline in mean number of occasions of rescue medication use/day 2-week mean • Mean number of days with oral corticosteroids (OCS) usage over 52 weeks • Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period • Change from baseline in Sino-nasal Outcomes Test-22 (SNOT-22) score at discrete timepoints during the 52-week period
• To investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient- and clinician-rated response to therapy • patient global impression of asthma severity and its change from baseline	• Patient-rated response to therapy at discrete timepoints during the 52-week period • Clinician-rated response to therapy at discrete timepoints during the 52-week period • Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period • Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during the 52-week period
• To investigate the PD effects of GSK3511294	• Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period

Objectives	Endpoints
• To investigate the PK of GSK3511294	• GSK3511294 plasma concentration at discrete timepoints during the 52-week period
Safety	
• To evaluate the safety and tolerability of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Incidence of AEs/SAEs • Laboratory parameters, including haematological and clinical chemistry parameters • Vital signs including blood pressure (BP), body temperature, and pulse rate • ECG assessments • Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294
Health Resource Use	
• To further evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on healthcare utilisation on top of existing asthma therapy	• Healthcare utilisation for asthma including hospitalisation, ED, and physician office/clinic visits

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

3.1. Primary Estimand

Population: Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Treatment comparison: GSK3511294 + SoC compared with placebo + SoC

Endpoint: Annualised rate of clinically significant exacerbations over 52 weeks

Main intercurrent events anticipated:

- Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e. regardless of the intercurrent event occurring
- Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be handled with a hypothetical strategy i.e. had the intercurrent event not occurred

- Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): to be handled with a treatment policy i.e. regardless of the intercurrent event occurring

Summary measure: Ratio of the rates of clinically significant exacerbations between GSK3511294 + SoC and placebo + SoC

For further details, see (Section 9.4

3.2. Secondary Estimands

Population: Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Treatment comparison: GSK3511294 + SoC compared with placebo + SoC

Endpoints:

- Change from baseline in SGRQ at Week 52
- Change from baseline in ACQ-5 at Week 52
- Change from baseline in pre-bronchodilator FEV_1 at Week 52
- Annualised rate of clinically significant exacerbations requiring hospitalisation and/or ED visit over 52 weeks

Main intercurrent events anticipated:

- Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e. regardless of the intercurrent event occurring
- Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be handled with a hypothetical strategy i.e. had the intercurrent event not occurred
- Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): to be handled with a treatment policy i.e. regardless of the intercurrent event occurring

Summary measures:

- Difference in mean change from baseline in SGRQ at Week 52
- Difference in mean change from baseline in ACQ-5 at Week 52
- Difference in mean change from baseline in pre-bronchodilator FEV_1 at Week 52
- Ratio of the rates of clinically significant exacerbations requiring hospitalisation and/or ED visit

between GSK3511294 + SoC and placebo + SoC.

For further details, see (Section 9.4)

4. STUDY DESIGN

4.1. Overall Design

This study employs a multi-centre, randomised, placebo-controlled, double-blind, parallel group design. The study will recruit adults and adolescents (≥12 years) with a confirmed diagnosis of severe asthma with an eosinophilic phenotype and who are on a regimen of medium to high dose ICS (≥440 mcg fluticasone propionate [FP] hydrofluoroalkane product [HFA] daily, or clinically comparable [GINA, 2020; see Appendix 10]) plus at least one additional controller medication, with evidence of bronchodilator reversibility or airway hyperresponsiveness as measured by methacholine/histamine challenge. Eligible participants must have uncontrolled asthma with a history of repeat exacerbations (≥2 exacerbations in the previous 12 months) while on their existing maintenance asthma therapy that excludes any biologics. Participants will be required to have a blood eosinophil count of ≥150 cells/µL at screening or ≥300 cells/µL documented in the 12 months prior to screening. Participants who have received any anti-IL-5/5R mAb therapy within the last 12 months will be excluded from this study.

Participants will attend a Pre-screen Visit (Visit 0) to sign consent and a Screening Visit (Visit 1; may be done on the same day as Visit 0) for eligibility assessments (see Section 8.1). At the conclusion of the run-in period (Visit 2), participants who meet the pre-defined criteria (see Section 5.1 and Section 5.3) will be randomised in a 2:1 ratio to receive either GSK3511294 100 mg or placebo, administered SC (at Week 0 and Week 26) in the clinic via a pre-filled safety syringe (PFS) as an adjunct therapy. Randomisation will be stratified based on baseline ICS dose (aiming to up to 50% approximately of participants on medium ICS dose; see Appendix 10). Participants will remain on their existing stable maintenance asthma therapy throughout the study (See Section 6.9 for details on concomitant medications). See Section 4.1.1 for additional details on the study phases, duration, and treatment arms.

The primary outcome measure will be the annualised rate of clinically significant exacerbations (i.e. exacerbations requiring systemic CSs and/or hospitalisation and/or ED visit [see Section 8.2.2]) measured over the 52-week treatment period. Additional efficacy assessments will include lung function (pre- and post-bronchodilator FEV_1), asthma control (ACQ-5), HRQoL measured with SGRQ, fatigue (PROMIS items), nasal symptoms (SNOT-22 questionnaire), daytime and night-time asthma symptoms (ADSD/ANSD), and daily electronic diary (eDiary) parameters including peak flow, rescue use, daily symptoms and nocturnal awakening due to asthma (see Section 8.2).

The study will include safety (see Section 8.3 and Section 8.4) and immunogenicity (see Section 8.8) assessments to characterise the safety profile of GSK3511294 100 mg SC following repeat dosing. In addition, blood samples will be collected for assessment of PD effects (blood eosinophils) (see Section 8.7) and PK of GSK3511294 (see Section 8.5).

After randomisation, all participants will be encouraged to remain in the study and complete all scheduled visits, regardless of whether they receive the second dose of study intervention at Week 26. Participants who experience any of the study intervention

discontinuation conditions (listed in Section 7.1) will not receive another dose of study intervention.

Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 3, Visit 10, Visit 11 Exit Visit 17, and WS Visit (if applicable). Participants who are unable to attend their scheduled clinic visits due to COVID-19 restrictions or other unexpected events may complete some visits at home (see Appendix 11). Note: study intervention will only be administered in the clinic (at Week 0 and Week 26 visits).

4.1.1. Study Phases, Duration and Treatment Arms

At pre-screening, participants will be requested to participate in the study for a maximum of 60 weeks (Visit 0 to the Exit Visit, inclusive) or 64 weeks if not continuing into the OLE Study 212895 (Visit 0 to the Follow-up Visit, inclusive).

During the study, participants will remain on their existing maintenance asthma therapy whilst completing all phases of the study described in Table 1.

Table 1 Study Phases

Phase	Phase Title	Duration	Description
1	Pre-screening (Visit 0)	0-2 weeks	Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) but must be completed prior to initiating any Visit 1 procedures
2	Screening (Visit 1) and Run-in	1-6 weeks	Participants who meet all the eligibility criteria at Screening (Visit 1) will enter the run-in period for a minimum of 1 week and a maximum of 6 weeks. The run-in is intended to assess the participant's compliance with study-related procedures and continued eligibility for the study as well as to collect baseline eDiary data. Participants who experience an asthma exacerbation during the run-in period should receive treatment for their exacerbation and remain in the run-in period until the investigator considers that the participant has returned to their baseline asthma status for at least one week. The participants that are not eligible to continue in the study at the end of the run-in period will be deemed run-in failures, but may be rescreened after consultation with the Medical Monitor (Section 5.5).

Phase	Phase Title	Duration	Description
3	Study Intervention (Visit 2-Visit 17)	52 weeks	Participants who meet the randomisation criteria will enter the 52-week treatment period and will be randomised to receive either add-on **GSK3511294 (100 mg) or matching placebo in a 2:1 ratio.** During the treatment phase, a total of 2 doses of study medication will be administered SC via PFS: at Week 0 (Visit 2) and Week 26 (Visit 10).[a] Study visits will occur at Week 0, Week 2, Week 4 and every 4 weeks thereafter with an additional study visit at Week 26 for the administration of the second dose of study intervention. The study intervention period will conclude with the Exit Visit at Week 52 (Visit 17).
Only participants who choose not to enter the OLE study will complete the phase below:			
4	Follow-up	4 weeks	Participants will complete a Follow-up visit/call 4 weeks after the Exit Visit; this visit/call will capture AE/SAE assessments and a urine pregnancy test result. At the end of the Follow-up visit/call, participants will be prescribed appropriate alternative asthma therapy at the physician's discretion, if required.

a. Participants who experience any of the study intervention discontinuation conditions listed in Section 7.1 will not receive another dose of study intervention but will be encouraged to remain in the study and complete their remaining scheduled visits/assessments.

4.1.2. Treatment after the End of Study

Participants who receive both doses of double-blind treatment and complete the Week 52 Exit Visit will be eligible to participate in the OLE study 212895. See Section 6.7 for details.

Participants who are not entering the OLE study 212895 will enter a 4-week follow-up period and complete the study with a Follow-up visit/call at Week 56. After study completion, appropriate alternative asthma therapy may be prescribed at the physician's discretion.

4.1.3. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilised in this study to ensure external objective review of the data in order to protect the ethical and safety interests of participants and to protect the scientific validity of the study (see Section 10.1.5).

4.2. Scientific Rationale for Study Design

Population: This study is designed to evaluate the efficacy and safety of GSK3511294 100 mg SC as an adjunct therapy in participants with severe uncontrolled asthma with an eosinophilic phenotype. Participants should have uncontrolled asthma, as evidenced by repeat exacerbations, despite treatment with optimised background therapy consisting of maintenance ICS treatment and at least one additional controller. Participants are also required to have the requisite elevated blood eosinophil count (see randomisation criterion 1, Section 5.3) that is indicative of asthma with an eosinophilic phenotype. This population has been shown to benefit from add-on anti-IL-5 therapies such as mepolizumab [Pavord, 2012, Ortega, 2014; Chupp, 2017] and is therefore anticipated to benefit from GSK3511294.

Blood eosinophil count screening: A Screening blood eosinophil count threshold of ≥150 cells/µL at Screening Visit 1 or ≥300 cells/µL in the previous 12 months has been selected as a criterion to identify participants likely to respond to treatment with anti-IL-5 therapy, consistent with findings from previous trials with mepolizumab.

Primary efficacy endpoint: A primary efficacy endpoint of annualised rate of clinically significant exacerbations has been selected as a robust and clinically relevant measure of the direct benefit of GSK3511294 to a population with severe uncontrolled asthma with an eosinophilic phenotype. In the current study, the definition of clinically significant exacerbations (see Section 8.2.2), i.e. exacerbations treated with systemic CSs (intramuscular [IM], intravenous [IV], or oral) for 3 or more days and/or hospitalisation and/or ED visit, is consistent with previous trials with mepolizumab [Pavord, 2012; Ortega, 2014] and reslizumab [Castro, 2015].

Placebo-control design: An established randomised, double-blind and parallel-group study design will allow for a robust determination of participant response to GSK3511294 as an adjunct therapy to their maintenance asthma therapy. As such, the comparator arm in this study will be placebo plus continued maintenance asthma treatment. A 2:1 randomisation will be used in order to limit the number of participants randomised to placebo treatment and to provide more safety information on GSK3511294. All participants will continue to receive their optimised and stable maintenance asthma therapy throughout the entire duration of the study regardless of intervention arm assignment. The stable maintenance asthma therapy (per the inclusion criteria) will consist of medium to high dose ICS (≥440 mcg FP HFA daily, or clinically comparable [GINA, 2020; see Appendix 10]) with at least one additional controller medication e.g., long-acting beta-2-agonist (LABA), with or without maintenance oral corticosteroids (OCS). Participants who are treated with medium dose ICS will also need to be treated with LABA to qualify for inclusion.

Study Duration: A 52-week treatment period should allow sufficient time to assess whether GSK3511294 100 mg SC, administered as two repeat doses 26 weeks apart (at Week 0 [randomisation] and at Week 26), can reduce the annualised rate of clinically significant exacerbations to a similar extent to that observed with other anti-IL-5 mAbs. The study will also provide 12-month safety data with repeat dosing.

Run-in Period: The one-week (maximum 6 weeks) Run-in period allows for the assessment of participant understanding and compliance with the daily eDiary, to establish Baseline symptoms, and to allow adequate time for receipt of results from assessments collected at Screening Visit 1.

Open-label extension study: Following study completion, all eligible participants will have the option to participate in the OLE study to provide additional safety data (see Section 6.7).

Data collection after discontinuation from study intervention: The protocol objective is to collect data over the full study period, whether participants continue on study intervention or in the case of premature discontinuation from study intervention. However, the decision to continue in the study after premature discontinuation from study intervention remains the prerogative of the participant. Participants who agree to continue in the study after premature discontinuation from study intervention (for any reason) will continue to be contacted by the study site, either through in clinic visits or by phone as agreed with the participant, on a monthly basis (aligned to their study schedule) until the end of their planned 52-week participation and follow up contact 4 weeks later, to enable capture of post-intervention information.

4.2.1. Participant Input into Design

Participant involvement in the study design was obtained from 10 patients (6 in Italy, 1 in UK, and 3 in US [1 adolescent]) using 2 online qualitative surveys containing 17 questions over a period of 2 weeks. Based on the participant feedback, the following design elements will be implemented:

- Reduced number of laboratory samples and patient-reported outcomes (PRO) assessments
- A hybrid trial model, allowing for home visits and virtual/telemedicine visits at key assessments which will reduce the burden of onsite visits and offer some flexibility in visit timing for the participant's schedule

4.3. Justification for Dose

The dose rationale for this study is supported by the FTIH Study 205722 [GlaxoSmithKline Document Number 2019N411063_00] that investigated single SC doses of GSK3511294 ranging from 2 mg to 300 mg. The FTIH study was designed to collect robust blood eosinophil pharmacology data (including washout) in a relevant population (mild to moderate asthma and a blood eosinophil count ≥200 cells/µL at screening) and inform dose selection in late-phase development using Model-informed drug development (MIDD) principles [Wang, 2019; Marshall, 2019]. The precedence of using blood eosinophil reduction as a predictor of efficacy in severe asthma with an eosinophilic phenotype was established in two mepolizumab Phase 3 studies, which consistently reduced annualised exacerbation rate by approximately 50%, for associated reductions in blood eosinophils of 84% in the MENSA trial [Ortega, 2014] and 78% in the MUSCA trial [Chupp, 2017], compared with placebo. Since GSK3511294 targets the same IL-5 epitope as mepolizumab, establishing the same reduction in blood eosinophils as mepolizumab via the same IL-5 neutralisation is expected to generate the same clinical

efficacy in the same patient population (i.e., severe asthma with an eosinophilic phenotype with a previous history of two or more exacerbations in the past 12 months). In addition, given the precedented safety profile of IL-5 neutralisation comparable to placebo, targeting previous mepolizumab pharmacology is both valid and expeditious in selecting the dose of GSK3511294.

A comprehensive analysis of the clinical effects of GSK3511294 on blood eosinophils from Study 205722 was therefore conducted to identify the dose and frequency of dosing that match previous Phase 3 mepolizumab target pharmacology most closely. To this end, a Bayesian non-linear mixed-effects dose-time response model was used to analyse blood eosinophil data. This model was then used to calculate the posterior probability of achieving reductions of 78% for the MUSCA trial [Chupp, 2017] and 84% for the MENSA trial [Ortega, 2014] compared with placebo. Doses deemed suitable were defined as having a probability of exceeding MUSCA in excess of 80% while doses deemed unsuitable as having a probability of exceeding MENSA of less than 10%.

Based on the comprehensive analysis of the clinical effects of GSK3511294 on blood eosinophils, a dose of 100 mg SC GSK3511294 administered every 26 weeks has been selected to match the pharmacology seen with mepolizumab in two Phase 3 studies at the approved therapeutic dose, but over an extended period of 26 weeks [GlaxoSmithKline Document Number 2019N418119_00].

4.4. End of Study and Study Completer Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed the visit at Week 52, regardless of whether the second dose of study intervention (at Week 26) was received.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if **all** of the following criteria apply:

AGE

1. **Age:** Adults and adolescents ≥12 years of age, at the time of signing the informed consent/assent.

   [For countries where local regulations or the regulatory status of study medication permit enrolment of adults only, participants recruited will be ≥18 years of age]

   Note: UK, Russia and German Participants: In UK, Russia and Germany only adult participants (≥18 years) are to be included in this clinical trial.

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS

2. **Asthma:** Participants must have a documented physician diagnosis of asthma for ≥2 years that meets the National Heart, Lung, and Blood Institute guidelines [NHLBI, 2007] or GINA guidelines [GINA, 2020] **AND**

   a) **Eosinophilic phenotype:** Have, or with high likelihood of having, asthma with an eosinophilic phenotype as per Randomisation Criteria 1 and 2 (see Section 5.3)

   AND

   b) **Exacerbation history:** Have previously confirmed history of ≥2 exacerbations requiring treatment with systemic CS (IM, IV, or oral), in the 12 months prior to Visit 1, despite the use of medium to high-dose ICS (see criterion 4). For participants receiving maintenance CS, the CS treatment for the exacerbations must have been a two-fold dose increase or greater.

3. **Airflow obstruction:** Persistent airflow obstruction as indicated by:

   a) For participants ≥18 years of age at Visit 1, a pre-bronchodilator FEV_1 <80% predicted (NHANES III) recorded at Visit 1

   b) For participants 12-17 years of age at Visit 1:

   - A pre-bronchodilator FEV_1 <90% predicted (NHANES III) recorded at Visit 1

     OR

   - FEV_1:Forced Vital Capacity (FVC) ratio <0.8 recorded at Visit 1

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4. **Inhaled Corticosteroid:** A well-documented requirement for regular treatment with medium to high dose ICS (in the 12 months prior to Visit 1 with or without maintenance OCS). The maintenance ICS dose must be ≥440 mcg FP HFA daily, or clinically comparable [GINA, 2020; see Appendix 10]. Participants who are treated with medium dose ICS will also need to be treated with LABA to qualify for inclusion.
5. **Additional Controller Medication:** Current treatment with at least one additional controller medication, besides ICS, for at least 3 months [e.g., LABA, long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonist (LTRA), or theophylline].

SEX

6. **Male or eligible female.**

   Female Participants:

   - A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
     - Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4.1

       OR
     - Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4.2 from at least 14 days prior to the first dose of study intervention until at least 30 weeks after the last administered dose of study intervention.
   - A WOCBP must have a negative highly sensitive serum pregnancy test at screening Visit 1 and a negative highly sensitive urine pregnancy test within 24 hours before the first dose of study intervention. Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.
   - Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
   - The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated in relationship to the first dose of study intervention).
   - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

SEX
Note: If the childbearing potential changes after start of the study (e.g., a premenarcheal female participant experiences menarche) or the risk of pregnancy changes (e.g., a female participant who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine if a female participant must begin a highly effective method of contraception. If reproductive status is questionable, additional evaluation should be considered.
INFORMED CONSENT
7. **Informed Consent:** Capable of giving signed informed consent/assent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. **French participants:** In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

MEDICAL CONDITIONS
1. **Concurrent Respiratory Disease:** Presence of a known pre-existing, clinically important lung condition other than asthma. This includes (but is not limited to) current infection, bronchiectasis, pulmonary fibrosis, bronchopulmonary aspergillosis, or diagnoses of emphysema or chronic bronchitis (chronic obstructive pulmonary disease other than asthma) or a history of lung cancer.
2. **Eosinophilic Diseases:** Participants with other conditions that could lead to elevated eosinophils such as hyper-eosinophilic syndromes including (but not limited to) Eosinophilic Granulomatosis with Polyangiitis (EGPA, formerly known as Churg-Strauss Syndrome) or Eosinophilic Esophagitis.
3. **Parasitic infection:** Participants with a known, pre-existing parasitic infestation within 6 months prior to Visit 1.
4. **Immunodeficiency:** A known immunodeficiency (e.g. human immunodeficiency virus – HIV), other than that explained by the use of CSs taken as therapy for asthma.
5. **Malignancy:** A current malignancy or previous history of cancer in remission for less than 12 months prior to screening (Participants that had localised carcinoma of the skin which was resected for cure will not be excluded).
6. **Liver Disease:** Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice.

MEDICAL CONDITIONS

NOTE: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) are acceptable if participant otherwise meets entry criteria.

7. **Other Concurrent Medical Conditions:** Participants who have known, pre-existing, clinically significant cardiac, endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.
8. **Vasculitis:** Participants with current diagnosis of vasculitis. Participants with high clinical suspicion of vasculitis at screening will be evaluated and current vasculitis must be excluded prior to enrolment.
9. **COVID-19:** Participants that, according to the investigator's medical judgment, are likely to have active COVID-19 infection should be excluded. Participants with known COVID-19 positive contacts within the past 14 days should be excluded for at least 14 days following the exposure during which the participant should remain symptom-free.

PRIOR/CONCOMITANT THERAPY

10. **Monoclonal antibodies targeting IL-5/5R:** Participants who have received mepolizumab (Nucala), reslizumab (Cinqair/Cinqaero), or benralizumab (Fasenra) within 12 months prior to Visit 1 or who have a previous documented failure with anti-IL-5/5R therapy.
11. **Other mAbs in the treatment of asthma**: Participants who have received omalizumab (Xolair) or dupilumab (Dupixent) within 130 days prior to Visit 1.
12. **Other mAbs not used for the treatment of asthma:** Participants who have received any mAb within 5 half-lives of Visit 1. Authorized treatments for COVID-19 are permitted.
13. **Investigational Medications:** Participants who have received treatment with an investigational drug within the past 30 days or five terminal phase half-lives of the drug whichever is longer, prior to Visit 1 (this also includes investigational formulations of marketed products).

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

14. **Previous participation:** Previously participated in any study with mepolizumab, reslizumab, or benralizumab and received study intervention (including placebo) within 12 months prior to Visit 1.

DIAGNOSTIC ASSESSMENTS
15. **ECG Assessment:** QTcF ≥450 msec or QTcF ≥480 msec for participants with Bundle Branch Block in the 12-lead ECG central over-read from screening Visit 1.

OTHER EXCLUSIONS
16. **Smoking history:** Current smokers or former smokers with a smoking history of ≥10 pack years (number of pack years = (number of cigarettes per day / 20) x number of years smoked). A former smoker is defined as a participant who quit smoking at least 6 months prior to Visit 1. 17. **Alcohol/Substance Abuse:** A history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1. 18. **Hypersensitivity:** Participants with allergy/intolerance to the excipients of GSK3511294 in Section 6.1 or any mAb or biologic. 19. **Pregnancy:** Participants who are pregnant or breastfeeding. Participants should not be enrolled if they plan to become pregnant during the time of study participation. Requirements for pregnancy testing are located in Section 8.3.5. 20. **Adherence:** Participants who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations.

5.3. Randomisation Criteria

At the end of the run-in period, study participants must fulfil all of the randomisation inclusion/exclusion criteria below in order to be randomised to study intervention.

5.3.1. Randomisation Inclusion Criteria

RANDOMISATION INCLUSION CRITERIA
1. **Blood eosinophil count:** a) An elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past 12 months prior to Visit 1 that is related to asthma **OR** b) An elevated peripheral blood eosinophil count of ≥150 cells/μL at Screening Visit 1 that is related to asthma. 2. **Asthma:** Evidence of airway reversibility or responsiveness as documented by either: a) Airway reversibility (FEV_1≥12% and 200 ml) demonstrated at Visit 1 or Visit 2 using the Maximum Post Bronchodilator Procedure **OR**

RANDOMISATION INCLUSION CRITERIA
b) Airway reversibility ($FEV_1 \geq 12\%$ and 200ml) documented in the 24 months prior to Visit 2 (randomisation visit) **OR** c) Airway hyperresponsiveness (methacholine: PC_{20} of <8 mg/mL, histamine: PD_{20} of <7.8 μmol, mannitol: decrease in FEV_1 as per the labelled product instructions) documented in the 24 months prior to Visit 2 (randomisation visit) 3. **eDiary compliance:** Compliance with completion of the eDiary defined as completion of all questions on 4 or more days out of the 7 days immediately preceding Visit 2.

5.3.2. Randomisation Exclusion Criteria

RANDOMISATION EXCLUSION CRITERIA

1. **Laboratory abnormality:** Evidence of clinically significant abnormality in the haematological, biochemical or urinalysis screen at Visit 1, as judged by the investigator.
2. **Liver chemistry test:** Participants who meet the following based on results from sample taken at Screening Visit 1:
   a) Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
   b) Total bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
   c) Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice.

   NOTES: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) is acceptable if the participant otherwise meets entry criteria.
3. **ECG:** QTcF ≥450msec, or QTcF ≥480 msec for participants with Bundle Branch Block, in the 12-lead ECG machine read at randomisation Visit 2 are excluded. Participants are excluded if an abnormal ECG finding from central over-read of the 12-lead ECG conducted at Screening Visit 1 is considered to be clinically significant and would impact the participant's participation during the study, based on the evaluation of the Investigator.
4. **Unstable Asthma:** Participants with a clinically significant asthma exacerbation in the 7 days prior to randomisation should have their randomisation visit delayed until the investigator considers the participant's asthma to be stable (see Section 5.6).
5. **Maintenance Asthma Therapy:** Any changes in the dose or regimen of baseline ICS and/or additional controller medication (except for treatment of an exacerbation) during the run-in period.

5.4. Lifestyle Considerations

No lifestyle restrictions are required for this study.

5.5. Pre-screen/Screen/Run-in Failures

Pre-screen/screen/run-in failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any SAEs.

For the purposes of this study, pre-screen/screen/run-in failures will be defined as follows:

Pre-screen Failures	Screen Failures	Run-in Failures
Participants who are assigned a study number at the time of signing the informed consent (pre-screen visit) but do not progress to the screening visit.	Participants who complete at least one additional Visit 1 (Screening) procedure but do not enter the run-in period.	Participants who enter the run-in period but are not subsequently randomised.

Re-screening of participants will be permitted; however, advance written approval to proceed with re-screening a participant must be obtained from the Medical Monitor.

Re-screened participants should be assigned a new participant number for every screening/rescreening event.

5.6. Criteria for Temporarily Delaying Randomisation

Participants who experience a clinically significant asthma exacerbation during the run-in period should receive treatment for their exacerbation, have their randomisation visit delayed and remain in the run-in period (up to 6 weeks) until the investigator considers the participant to have returned to their baseline asthma status for at least 7 days.

A clinically significant exacerbation is defined as worsening of asthma requiring the use of systemic CS and/or hospitalisation and/or ED visit (Section 8.2.2).

A participant who is not eligible to continue in the study at the end of the run-in period, should be considered a run-in failure but may be rescreened after consultation with the Medical Monitor (Section 5.5).

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s)/product(s) (IP), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Study intervention will only be administered in the clinic; hence Visit 2 (Week 0) and Visit 10 (Week 26) are required to be in-clinic visits.

6.1. Study Intervention Administered

GSK3511294 is a humanised IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. GSK3511294 liquid drug product will be supplied by GSK in a Type I glass syringe (with a 1/2-inch, 29-gauge thin wall, staked needle and sealed with a latex-free rubber plunger). The drug product and syringe will be assembled in a single use, disposable safety syringe to enable delivery of the drug product. Each device enables SC delivery of 100 mg GSK3511294 in 1.0 mL sterile liquid formulation. The formulation contains L-histidine, trehalose dihydrate, L-arginine hydrochloride, disodium edetate (EDTA), water for injection and polysorbate 80.

The placebo in this study will be 0.9% sodium chloride solution contained in a PFS also supplied by GSK.

An overview of study intervention is provided in Table 2.

Table 2 Overview of Study Intervention

ARM Name	GSK3511294 100 mg	Placebo
Intervention Name	GSK3511294 100 mg SC	Placebo
Type	Biologic	N/A
Dose Formulation	Sterile liquid formulation in single-use PFS	Sterile 0.9% (w/v) sodium chloride solution in single-use PFS
Unit Dose Strength(s)	100 mg/mL; 1.0 mL (deliverable)	N/A, 1.0 mL (deliverable)
Dosage Level(s)	100 mg once every 26 weeks (Week 0 and Week 26)	Placebo once every 26 weeks (Week 0 and Week 26)
Route of Administration	SC injection	SC injection
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor

ARM Name	GSK3511294 100 mg	Placebo
Packaging and Labelling	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.

PFS=Pre-filled safety syringe, IMP=Investigational Medicinal Product, N/A=not applicable

6.1.1. Medical Devices

The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are injection devices:

- A pre-filled syringe contained within a safety syringe. The devices used in the study are representative of the devices planned to be marketed for the product.
- The components that comprise the pre-filled syringe (glass barrel with pre-staked needle and plunger) are sourced from Becton Dickinson. The pre-filled syringe is filled with study intervention (GSK3511294 or placebo) and assembled at GSK, Barnard Castle.
- The safety syringe components are manufactured by Becton Dickinson. The safety syringe components are assembled with the pre-filled syringe at GSK, Barnard Castle.

The Instruction for use (IFU) of the injection device will be provided. The instructions were developed and optimised as a result of formative human factors studies for mepolizumab and are representative of those that are planned for GSK3511294.

All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the investigator throughout the clinical investigation (see Section 8.4.8) and appropriately managed by GSK.

6.2. Packaging and Labelling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.3. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention.
- All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the SRM.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.4. Measures to Minimise Bias: Randomisation and Blinding

6.4.1. Treatment Assignment

- Eligible participants will be centrally randomised using an IRT system.
- The randomisation schedule will be generated using the GSK validated randomisation software RandAll NG. Separate randomisation schedules will be created for each country. Participants will be assigned to study intervention in accordance with the randomisation schedule. Once a randomisation number has been assigned to a participant, it cannot be reassigned to any other participant in the study.
- Randomisation will be stratified according to the participant's baseline ICS dose (aiming to up to 50% approximately of participants on medium ICS dose; see Appendix 10).
- At Visit 2 (Week 0), those participants who meet the randomisation criteria will be randomised in a 2:1 ratio to receive one of the following study treatments in addition to their stable maintenance asthma treatment:
    - GSK3511294 100 mg SC
    - Placebo SC
- Study intervention will be administered in the clinic at Visit 2 (Week 0) and Visit 10 (Week 26) as per the SoA (Section 1.3).

6.4.2. Blinding

- The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could

delay emergency intervention of the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.

- Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, GSK3511294 and placebo will be administered from PFSs that will be identical in appearance.
- If a participant's intervention code is unblinded by the investigator or treating physician, that participant will continue with all study visits but will not receive the second dose of study intervention at Week 26. The primary reason for the event or condition which led to the unblinding will be recorded in the CRF (see Section 7.1).
- To maintain the blind, haematology data (absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes) from post-randomisation samples will not be reported to the site or the central study team.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4.3. Controlled Early Access to Unblinded PK and PKPD Data

Designated independent representative(s) may be unblinded for performing population PK and PKPD dataset preparation and draft PK and PKPD model development using scrambled (random reassignment of subject identification numbers) PK and PKPD unblinded datasets, including baseline demographic characteristics. No adverse event data or efficacy data will be included.

6.5. Study Intervention Compliance

Both doses of GSK3511294 or placebo will be administered under medical supervision via SC injection to participants by the investigator or designee at the study site. Dose administration details (date and time) will be recorded in the source documents and reported in the CRF.

Participants will be monitored in clinic for a minimum of 2 hours post-dose to monitor for immediate hypersensitivity and any other untoward effects. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of GSK3511294, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care if appropriate.

6.6. Dose Modification

Dose modification is not allowed.

6.7. Continued Access to Study Intervention after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition whether or not GSK is providing specific post-study treatment.

At the end of the study, participants will be eligible to screen to enter the OLE Study 212895 and have continued access to open-label GSK3511294 if he/she:

- has received both doses of study intervention (at Week 0 and Week 26), AND
- completed the scheduled Exit Visit at Week 52, AND
- did not meet any of the study intervention discontinuation conditions (Section 7.1) during the study.

For participants who enrol into the 12-month OLE study, the Day 1 visit of the OLE study can occur on the same day as the Exit Visit of the current study. Specific details on the OLE study will be documented separately.

Participants who do not enter the OLE study will complete a follow-up visit/call and be prescribed alternative asthma therapy if needed and as determined by the study investigator.

6.8. Treatment of Overdose

The dose of GSK3511294 that is considered to be an overdose has not been defined. There are no known antidotes and there is no specific treatment for a suspected overdose. In FTIH study 205722 (refer to the current IB [GlaxoSmithKline Document Number 2016N295843_03 or later]), single SC doses of GSK3511294 up to 300 mg were well tolerated by adult participants with mild/moderate asthma (6 participants received a 300 mg SC dose).

Each PFS will enable the delivery of a single dose of study intervention (see Section 6.1). In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Treat the participant with active supportive care as dictated by the participant's clinical status in the knowledge of the long half-life (approximately 41 days) of GSK3511294.
- Closely monitor the participant for AE/SAE and laboratory abnormalities for 30 weeks following the last administered dose.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding discontinuation or delay of another dose of study intervention will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.9. Concomitant Therapy

At pre-screening and/or screening, information on the participant's baseline maintenance asthma therapy will be collected and recorded in the eCRF.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded in the eCRF along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency (any dose changes are to be recorded for OCS)

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Permitted Medications and Non-Drug Therapies

Throughout the study, participants are to be maintained on their baseline maintenance asthma treatment consisting of ICS plus at least one other controller, e.g. LABA, LAMA, with or without maintenance OCS (see inclusion criteria 4 and 5, Section 5.1). It is recognised that in a year-long study, changes may need to be individualised if clinically crucial for a participant. The investigator is encouraged to discuss any cases with the Medical Monitor before initiating changes to a participant's maintenance asthma medication.

Additional asthma medications such as theophyllines and anti-leukotrienes will be permitted as maintenance provided that they have been taken regularly in the 3 months prior to screening (Visit 1). If uncertain whether a medication is permitted, please confirm with the Medical Monitor.

Albuterol/salbutamol is permitted throughout the study but should be withheld in the 6-hour period prior to spirometry assessments, if possible. Study-provided albuterol/salbutamol should not be recorded in the eCRF, only in the eDiary.

LABAs, LAMAs, and fixed dose combinations of ICS/LABA or ICS/LABA/LAMA should be withheld for ≥12 hours prior to spirometry, if possible.

Continuous Positive Airway Pressure (CPAP) or Bilevel Positive Airway Pressure (BiPAP) for the treatment of obstructive sleep apnoea is permitted, if initiated prior to the Screening Visit (Visit 1). This treatment must be captured in the eCRF.

Allergen-specific immunotherapy is permitted provided that it has been taken regularly in the 6 months prior to screening (Visit 1).

Participants can be vaccinated against SARS-CoV-2 infection using authorized COVID-19 vaccines in line with local/national guidelines for COVID-19 vaccines. Experimental COVID-19 vaccines are not permitted.

COVID-19 vaccine administration and the administration of the study intervention should be separated by 14 days if possible, in order to be able to properly assess study injection site/treatment reactions.

Participants can be treated for SARS-CoV-2 infection using authorized COVID-19 treatments (including monoclonal antibodies) in line with local/national guidelines. Experimental COVID-19 treatments are not permitted.

6.9.2. Prohibited Medications and Non-Drug Therapies

The following medications are not allowed prior to screening (Visit 1), according to the following schedule, or during the study:

Medication	**Washout Time Prior to Screening Visit**
Investigational drugs	1 month or 5 half-lives whichever is longer
Omalizumab [Xolair], dupilumab [Dupixent]	130 days
Mepolizumab [Nucala], reslizumab [Cinqair/Cinqaero], benralizumab [Fasenra]	12 months
Other monoclonal antibodies	5 half-lives
Experimental anti-inflammatory drugs (non biologicals)	3 months

Immunosuppressive medications such as those listed below (not all inclusive)
Corticosteroids if used to treat a condition other than asthma • Intramuscular, long-acting depot • Regular systemic (oral or parenteral)
Methotrexate, cyclosporin, azathioprine
Oral gold
Chemotherapy used for conditions other than asthma

Additionally, Bronchial Thermoplasty and Radiotherapy are excluded for 12 months prior to Visit 1 and throughout the study. CPAP, BiPAP, and oxygen therapy should not be initiated during the run-in period.

6.9.3. Rescue Medicine

Trade label albuterol/salbutamol metered dose inhalers (MDIs) will be provided as rescue medication throughout the study. Albuterol/salbutamol will be sourced for all centres. Use of low dose ICS-formoterol as rescue medication is not allowed during the study.

Participants will be dispensed an MDI at Screening Visit 1 to be used primarily to treat asthma symptoms on an as needed basis and also during the reversibility assessments (see Section 8.2.3.1). The MDI should be replaced as needed.

Although the use of rescue medications is allowable (at any time during the study), the use of rescue medications should be withheld, if possible, for at least 6 hours prior to the spirometry assessments. Rescue medication usage will be recorded in the eDiary.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

No further doses of study intervention will be administered to participants who meet any of the following permanent treatment discontinuation conditions at any time during the study treatment period:

- Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria (see Section 7.1.1)
- ECG: Meets any of the protocol-defined QTc stopping criteria (see Section 7.1.2)
- Pregnancy: Positive pregnancy test (see Section 8.4.5)
- Severe allergic reaction/anaphylaxis: Participants with severe allergic reaction/anaphylaxis with no clear alternative cause (see Appendix 8)
- Vasculitis: Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation (see Section 7.5).
- Study treatment unblinded: Unblinding of the study treatment assigned to a participant (see Section 6.4.2).

If a participant meets any of the treatment discontinuation conditions or chooses (for any reason) not to receive another dose of study intervention before the end of the protocol specified randomised intervention period:

- The investigator will make every effort to encourage the participant to remain in the study **and** to continue with all remaining study visits, including the Exit and Follow-up Visits.
- The primary reason for discontinuation of study intervention (e.g., AE, lack of efficacy, protocol deviation, investigator discretion, consent withdrawn etc.) must be recorded in the eCRF.
- Participants will be provided with the option to continue their scheduled visits in-clinic, at home, or by phone. The required study assessments will depend on whether the participant is attending the visit in-clinic, at home, or by phone. At a minimum, an assessment of exacerbations, AEs, SAEs, and concomitant medications will be completed.
- If for any reason, the participant later chooses to withdraw from the study, a Withdraw from Study Visit (see Section 7.2) should be conducted according to the SoA (Section 1.3).

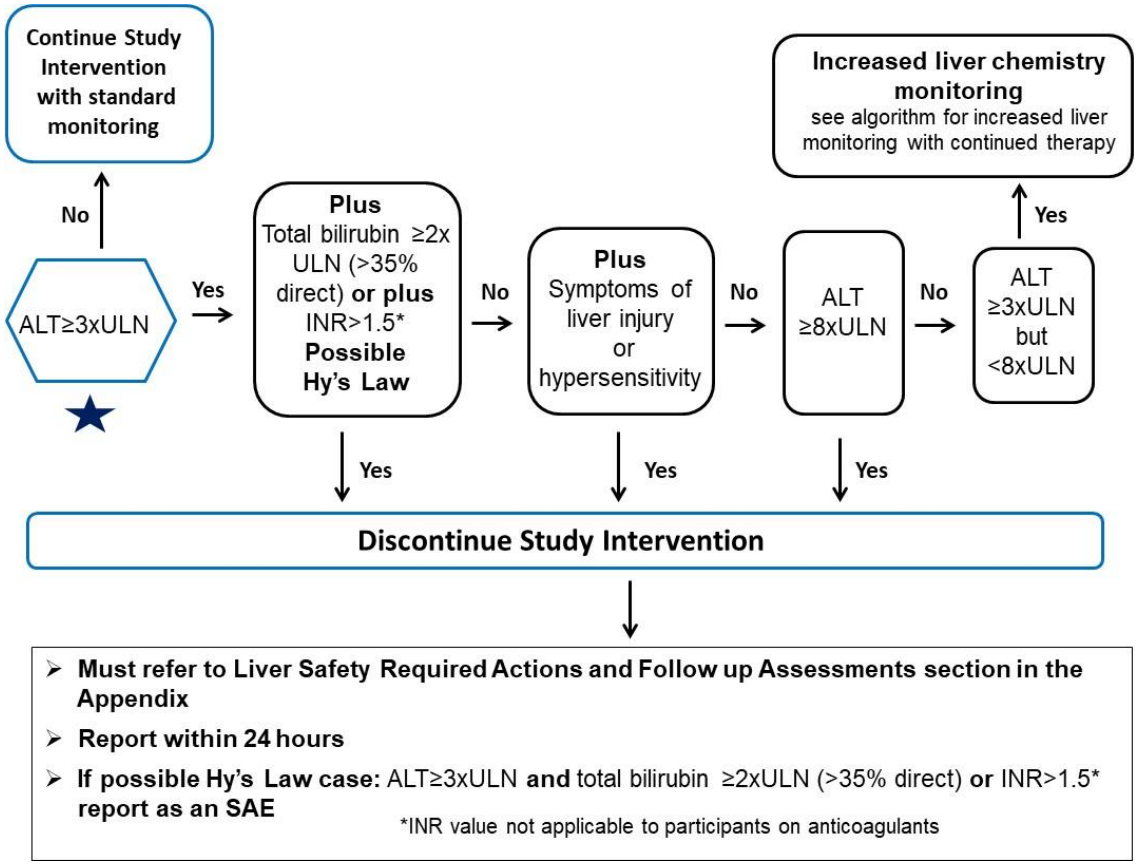
7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping criteria, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, the investigator believes that it is in the best interest of the participant.

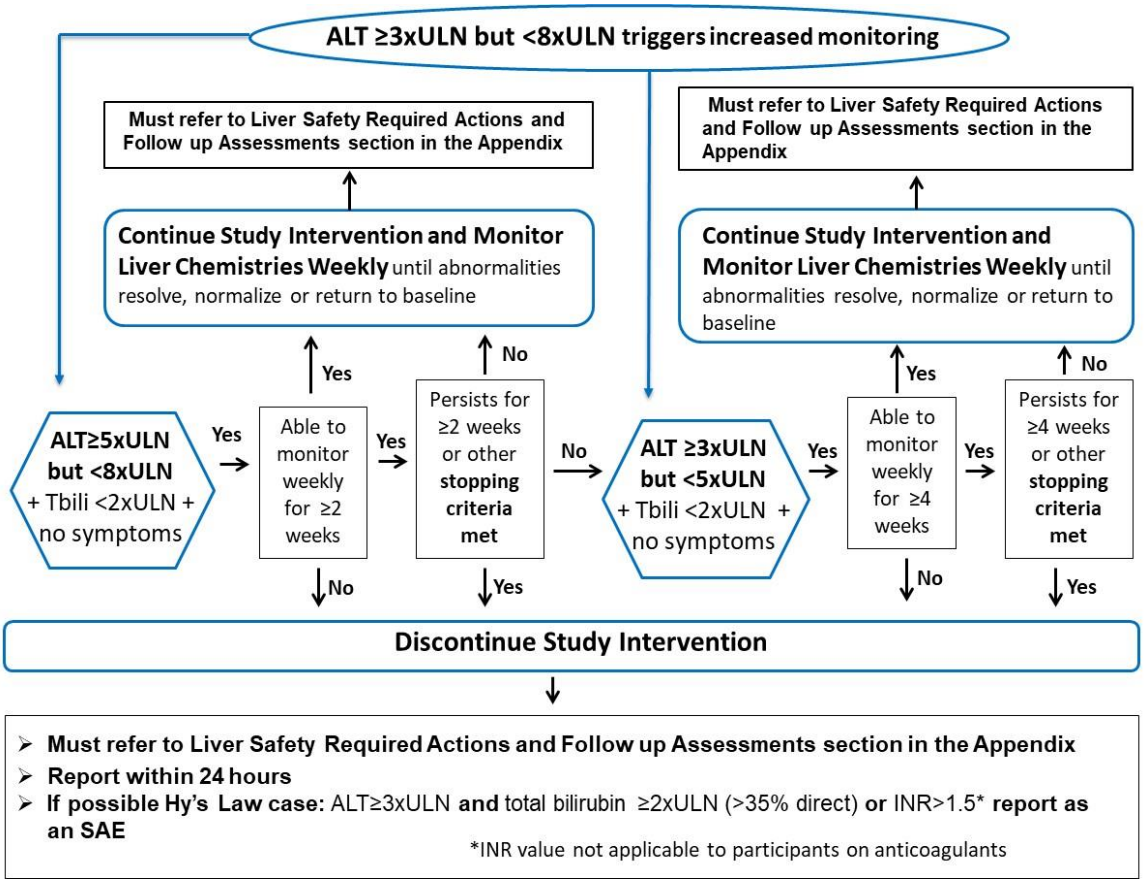
Liver Chemistry Stopping Criteria Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalised ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin

Refer to Appendix 6 for required Liver Safety Actions, Monitoring, and Follow-up Assessments.

Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT ≥3xULN but <8xULN and do not meet any of the liver stopping criteria



Abbreviations: ALT = alanine transaminase; Tbili = total bilirubin; INR = international normalised ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin.

Refer to Appendix 6 for required Liver Safety Actions, Monitoring and Follow-up Assessments.

7.1.1.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by a participant in this study will not be permitted.

7.1.2. QTc Stopping Criteria

Details on performing ECG assessments can be found in Section 8.3.3.

The QT interval corrected using Fridericia's formula (QTcF) must be used for *each individual participant* to determine eligibility for and discontinuation from the study intervention. This formula may not be changed or substituted once the participant has been enrolled.

For this study, the following QTc stopping criteria will apply:

- QTcF >500 msec OR uncorrected QT >600 msec
- Change from baseline of QTcF >60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTcF with Bundle Branch Block	**Discontinuation QTcF with Bundle Branch Block**
<450 msec	>500 msec
450 – 480 msec	≥530 msec

The QTcF value from the 12-lead ECG central over-read at randomisation Visit 2 should be used as baseline QTcF value for any changes from baseline calculations during the study. After randomisation 12-lead ECG central over-read values should be used to assess QTc stopping criteria, with the exception of Visit 10 (Week 26) where 12-lead ECG machine read values should be used.

7.1.3. Temporary Discontinuation

For this study, a temporary discontinuation refers to a delayed administration of the second dose of study intervention at Week 26.

If a participant becomes infected (parasitic infection) during the study intervention period before receiving the second dose of study intervention and does not respond to anti-helminth treatment, a delayed administration of the study intervention may be considered in consultation with the GSK Medical Monitor.

7.2. Participant Discontinuation/Withdrawal from the Study

- Participants are strongly encouraged to remain in the study for the entire duration but may prematurely withdraw from the study at any time at his/her own request, at the request of their legally authorised representative (LAR), or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.
- Participants who prematurely withdraw from the study should attend:
  - a Withdraw from Study (WS) Visit, 26 weeks after the last administered dose of study intervention (at Week 26 or Week 52) **AND**
  - a Follow-up visit/call, 30 weeks after the last administered dose of study intervention for AE/SAE and pregnancy assessments.

  Note: this includes any participants who initially discontinue study intervention and remain in the study (Section 7.1) but later decide to withdraw from the study.

- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits (or scheduled phone calls, if applicable) and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study. A final attempt will be made to contact the participant for a safety follow-up 30 weeks after the last administered dose of study intervention.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

7.4. Reasons for Study Intervention Discontinuation and/or Study Withdrawal

The primary reason for study intervention discontinuation and/or study withdrawal will be recorded in the eCRF. When a participant withdraws consent, the investigator must document the reason (if specified by the participant) in the eCRF.

7.5. Criteria for Follow-up of Potential Type III Hypersensitivity (Immune Complex Disease /Vasculitis)

Owing to the adverse findings of arterial inflammation that were observed in the 1-month, but not 6-month, nonclinical toxicology studies, events potentially representing type III hypersensitivity/immune complex disease/vasculitis should be promptly reported to GSK, and consultation with the Medical Monitor is encouraged. Treatment for the event will be given as medically required. If possible, PK, ADA, C3, and C4 samples

may be taken at the time of the event along with haematology, clinical chemistry and urinalysis.

Symptoms potentially suggestive of vasculitis include but are not limited to:

- persistent* fever (*where persistent is considered to be a duration of ≥2 days)
- persistent* muscle and joint pain
- persistent* rash
- persistent* fatigue
- symptoms of peripheral neuropathy, like numbness or weakness
- laboratory abnormalities, e.g., decreased platelets, elevated creatinine, decrease in complement C3/C4, abnormal urinary albumin/creatinine ratio

Participants who experience any of the above events should be monitored until the event resolves and/or a diagnosis is established.

The symptoms and clinical features are often non-specific and heterogenous with respect to the time course over which they develop, organ involvement and the constellation of symptoms and severity. Early recognition of potential events of vasculitis is important to timely diagnosis and subsequent treatment.

The precise management will depend on the clinical evaluation at the time of presentation and ongoing assessment including consideration of relevant differential diagnoses. Given that there is often a differential for presenting symptoms such as infection, and indeed such factors may also precipitate immune related AEs, these factors (infectious, neoplastic, metabolic, toxic) should be given due consideration and ruled out.

Serological, immunological, and histological (biopsy) data should be considered to support the diagnosis and consultation with the GSK Medical Monitor, and an appropriate medical specialist should be considered when investigating a possible immune related AE.

Unscheduled PK, ADA, C3 and C4 samples may be taken at the time of the event and samples may be taken for additional biomarkers (e.g., antinuclear antibodies [ANA], anti-neutrophil cytoplasmic antibodies [ANCA]) in the setting of clinical concern regarding the possibility of immune complex disease. If necessary, testing for biomarkers, e.g., ANA, ANCA (anti-myeloperoxidase [MPO] antibody and anti-proteinase 3 [PR3] antibody), may also be conducted using the frozen baseline serum samples (that were collected and stored prior to administration of study intervention) to allow for evaluation of interval change for participants with suspected vasculitis (see Section 8.7.2). Other possible causative or differential factors for abnormal clinical or laboratory observations may also have to be investigated including testing to exclude infection.

If clinically indicated, the participant may be referred to a specialist for further management, which may include organ biopsy.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Section 1.3).
- As detailed in the SoA (Section 1.3), participants who are not entering the OLE study 212895 should make every effort to complete the Week 56 follow-up visit/call on the scheduled day. The visit may be completed within 7 days of the scheduled time-point.
- Every effort should be made to reduce missing data throughout the study.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue to receive the second scheduled dose of study intervention, if applicable.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilised for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Laboratory results that could unblind the study (e.g., haematology differential [absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes]) will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Participants should be provided a quiet space in which to complete patient-reported outcomes (PRO), prior to other assessments and procedures. Site staff can provide limited advice if required, however participants should not be guided or directed in answering questions. Family or friends should not influence the answers. Site staff should encourage participants to complete all questions.

8.1. Screening and Critical Baseline Assessments

8.1.1. Pre-screening Visit (Visit 0)

Informed consent should be obtained at the Pre-screening Visit or the Screening Visit, prior to initiating any study assessments. A participant number will be assigned at the time the ICF is signed. Participants can conduct the Pre-screening Visit (Visit 0) up to 2 weeks prior to the Screening Visit (Visit 1).

The pre-screening procedures will include a review/assessment of:

- Inclusion/exclusion criteria (see Section 5.1 and Section 5.2)
- Demographic information including gender, ethnic origin, race, and year of birth (can be conducted at Visit 1 instead, if necessary)
- Childbearing status for all women (can be conducted at Visit 1 instead, if necessary); for WOCBP, contraception should be started at least 14 days prior to receiving the first dose of study intervention (see Appendix 4)
- Therapy history and concomitant medications including maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications

All clinic visits from Pre-screening Visit 0 to the Exit Visit (or if applicable, the WS Visit or the Follow-up Visit) should be completed in the relevant eCRF form. Visit 1, 2, 10 and WS visit must be registered in the IRT.

Serious adverse events must be collected from signing of Informed Consent if considered related to study procedures.

8.1.2. Critical Assessments performed at Screening (Visit 1)

The following critical assessments will be conducted at Screening Visit 1:

- Review inclusion/exclusion criteria (see Section 5.1 and Section 5.2)
- Review therapy history and concomitant medications including maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications.
- Medical history including:
  - Asthma including current treatment, duration of asthma, courses of rescue CSs, history of previous intubations, asthma exacerbation history in previous year, asthma triggers
  - Cardiovascular (CV) medical history/risk factors (as detailed in the eCRF)
  - Vasculitis, allergies and anaphylaxis history
  - Smoking history and current status
  - Historical blood eosinophil count - participants without a documented blood eosinophil count ≥300 cells/μL in the 12 months prior to Screening Visit 1 must show a blood eosinophil count ≥150 cells/μL, based on the sample collected at Visit 1 (see randomisation criterion 1, Section 5.3.1). If the Screening Visit test result does not meet the blood eosinophil count eligibility criteria, the laboratory assessment may be repeated, at the discretion of the investigator, if it is judged to be likely in the eligible range for study inclusion within the run-in period prior to Visit 2.
- Spirometry including bronchodilator responsiveness testing using the Maximum Bronchodilator Procedure (see Section 8.2.3). If a patient fails the protocol-specified reversibility criterion or FEV_1 inclusion criteria, spirometry retest is allowed during the run-in period.

- PGI-S (see Section 8.2.8)
- Safety Assessments including:
  - Physical exam (see Section 8.3.1)
  - Vital signs (see Section 8.3.2)
  - Resting 12-lead ECG (see Section 8.3.3)
  - AE/SAE assessment
- Blood/urine sample collection for the following laboratory tests (see Section 8.3.4):
  - Haematology with differential
  - Clinical chemistry (including liver chemistry)
  - Serum pregnancy test – for all WOCBP (childbearing potential for all women will be assessed at pre-Screening) (see Section 8.3.5)
  - Urinalysis (can be conducted at Visit 2 instead, if necessary)
  - Parasitic screening (only in regions with high-risk or for participants who have visited a high-risk region in the past 6 months)
- eDiary registration and training
- Provide medical problems and healthcare utilisation worksheet (see Section 8.9)
- Complete ADSD/ANSD (to be completed daily at home; see Section 8.2.10)

8.1.3. Critical Assessments performed at Randomisation (Visit 2)

The following critical assessments will be conducted at randomisation Visit 2:

- Review of randomisation criteria (see Section 5.3), and data collected at Visit 1, including, if applicable, verification that the asthma-related peripheral blood eosinophil count is ≥150 cells/μL, based on the sample collected at Visit 1
- Review of concomitant medications
- Spirometry (if airway reversibility was not demonstrated at Visit 1, the Maximum Bronchodilator Procedure may be repeated at Visit 2) (see Section 8.2.3)
- SGRQ (see Section 8.2.4)
- ACQ-5 (see Section 8.2.5)
- SNOT-22 (see Section 8.2.7)
- Review eDiary asthma symptoms and PEF summary report
- PGI-S (see Section 8.2.8)
- Safety assessments including:
  - Vital signs (see Section 8.3.2)
  - Resting 12-lead ECG (see Section 8.3.3)

  - AE/SAE assessment
- Blood/urine sample collection for the following laboratory tests (see Section 8.3.4):
  - Haematology with differential
  - Total IgE
  - Clinical chemistry (including liver chemistry)
  - Urine pregnancy test – for all WOCBP (see Section 8.3.5)
  - Complement C3 and C4
  - PK (see Section 8.5)
  - Baseline immunogenicity (see Section 8.8)
  - Storage of a baseline sample that may be analysed for the presence of ANCA (anti-MPO antibody and anti-PR3 antibody tests), ANA, and anti-dsDNA antibody, if necessary (see Section 7.5)
  - Storage of a baseline sample (with the participant's consent and where permitted) that may be analysed for exploratory biomarkers (see Section 8.7.3)
- Provide and review medical problems and healthcare utilisation worksheet (see Section 8.9)

The following items will be completed at home:

- PROMIS Items (see Section 8.2.6)
- Complete ADSD/ANSD daily (see Section 8.2.10)

8.2. Efficacy Assessments

8.2.1. Efficacy Endpoints

Efficacy endpoints and estimands are provided in Section 3.

8.2.2. Asthma Exacerbations

Clinically significant exacerbations of asthma are defined by:

Worsening of asthma which requires use of systemic CSs[1] and/or hospitalisation and/or Emergency Department (ED) visit.

[1]For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

Details of each asthma exacerbation, including medications used to treat exacerbations should be recorded in the eCRF.

Asthma exacerbations should not be recorded as an AE unless they meet the definition of a SAE.

The time period for collection of exacerbation information in the eCRF will be from the start of study intervention until the Exit Visit or Follow-up Visit if applicable.

8.2.3. Pulmonary Function Testing/ Spirometry

Spirometry lung function assessments will be performed for all participants at specified visits to assess FEV_1. At least 3 valid spirometry efforts should be attempted (with no more than 8 attempts) using the ATS guidelines [Miller, 2005]. Spirometry includes FEV_1, percent predicted FEV_1, Forced Vital Capacity (FVC) and FEV_1/FVC. Spirometry assessments will be performed at screening (Visit 1), randomisation (Visit 2), and at scheduled in-clinic visits according to the SoA (Section 1.3). At each visit, spirometry should be performed at the same time of day (±1 hour) as the assessment performed at Visit 2 (the baseline assessment). Participants should try to withhold short-acting beta-2-agonists (SABAs) for ≥6 hours and LAMAs/LABAs for ≥12 hours prior to the clinic visit, if possible.

Spirometry should not be conducted for participants with confirmed/suspected COVID-19.

8.2.3.1. Reversibility using the Maximum Post-Bronchodilator Method

Pre-bronchodilator measurements will be taken at the clinic visits specified in the SoA (Section 1.3): at screening, randomisation, Week 26 Visit, and Exit Visit (or EW Visit). In addition, post-bronchodilator values will be recorded following reversibility testing using the Maximum Post-Bronchodilator Method. Participants' reversibility will be assessed at Visit 1 (Screening). For participants unable to achieve ≥12% reversibility and 200 mL change at Visit 1, reversibility can be repeated at Visit 2 to confirm eligibility for the study (see randomisation criterion 2, Section 5.3.1). The procedures involved in the Maximum Post-Bronchodilator Method are those generated by the Pulmonary Physiology Subcommittee [Tepper, 2012]. Additional details on the reversibility testing procedures using the Maximum Post-Bronchodilator Method can be found in the spirometry section of the SRM.

8.2.4. St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a well-established instrument, comprising 50 items designed to measure Quality of Life in participants with diseases of airway obstruction [Jones, 1992]. The questionnaire will be administered as per guidance from the measure developers and completed electronically according to the SoA (Section 1.3).

8.2.5. Asthma Control Questionnaire-5 (ACQ-5)

The ACQ-5 is a five-item questionnaire, which has been developed as a measure of participants' asthma control that can be quickly and easily completed [Juniper, 2005]. The questions are designed to be self-completed by the participant. The five questions enquire about the frequency and/or severity of symptoms (nocturnal awakening on waking in the morning, activity limitation, and shortness of breath, wheeze) over the previous week. The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. This will be completed electronically according to the SoA (Section 1.3).

8.2.6. PROMIS Fatigue Items

The PROMIS Fatigue Item Bank includes a number of items assessing concepts from mild tiredness to exhaustion [Christodoulou, 2008; Cella, 2016]. A small number of individual questions assessing the concept of "Energy" from the PROMIS Fatigue item bank will be administered. Participants will complete these items on an electronic handheld device.

The PROMIS fatigue items should only be administered to participants for whom an appropriate translation is available (see the SRM for further details).

8.2.7. Sino-nasal Outcomes Test-22 (SNOT-22)

The SNOT-22 is a 22-item self-administered questionnaire to measure disease-specific quality of life of chronic rhinosinusitis (with or without nasal polyposis). The SNOT-22 contains questions about a broad range of health and HRQoL problems including physical problems, functional limitations and emotional consequences. The questions are designed to be self-completed by the participant [Hopkins, 2009]. The participant is asked to rate the severity of each item over the previous 2 weeks on a scale from 0 (no problem) to 5 (problem as bad as it can be). Responses to the questionnaire will be captured electronically.

The SNOT-22 questionnaire should only be administered to participants for whom an appropriate translation is available (see the SRM for further details).

8.2.8. Patient Global Impression of Asthma Severity/Change (PGI-S, PGI-C)

Patient Global Impression of Asthma Severity (PGI-S): The participant will complete a PGI-S question at Randomisation and visits according to the SoA (Section 1.3). This single global question will ask participants to rate their asthma severity on a five-point scale (no symptoms, mild, moderate, severe, very severe). Responses will be captured electronically.

Patient Global Impression of Change (PGI-C) from Baseline of Asthma Severity: The participant will complete a PGI-C question from baseline of their asthma severity at the visits specified in the SoA (Section 1.3). The single question will ask participants to rate the overall change in their asthma severity compared with Day 1 (randomisation) prior to start of study intervention. The rating will use a five-point scale (much better, a

little better, no change, a little worse, much worse) and responses will be captured electronically.

The PGI-S/PGI-C questionnaire should only be administered to participants for whom an appropriate translation is available. Additional instructions will be provided in the SRM.

8.2.9. Clinician/Patient Rated Response to Therapy

This is an overall evaluation of response to treatment, conducted separately by the investigator and the participant using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse

The evaluations will be completed electronically at the visits specified in the SoA (Section 1.3).

8.2.10. Asthma Daily Symptom Diary/Asthma Nightly Symptom Diary (ADSD/ANSD)

The ADSD/ANSD is a 6-item self-administered patient-reported diary developed by the PRO Consortium's Asthma Working Group (in accordance with the Food and Drug Administration's PRO Guidance) to facilitate comprehensive and reliable assessment of asthma symptoms from a patient's perspective [Gater, 2016].

The ADSD/ANSD is intended for use by adults and adolescents (aged 12 years and older) who are diagnosed with asthma to rate the severity of their symptoms in the three core categories: breathing symptoms (wheezing, shortness of breath), chest symptoms (chest tightness, chest pain) and cough.

The ADSD/ANSD must be completed twice daily by the participant:

- ADSD is to be completed before going to bed and refers to asthma symptoms during the day.
- ANSD is to be completed upon waking and refers to asthma symptoms during the previous night.

Participants are required to rate the six symptoms at their worst during the respective timeframes using an 11-point numeric rating scale (NRS) ranging from 0 ('None') to 10 ('As bad as you can imagine'). Responses will be captured electronically.

The ADSD/ANSD questionnaire should only be administered to participants for whom an appropriate translation is available. Further details are contained in the SRM.

8.2.11. eDiary Asthma Parameters and Alerts

The participant will be asked to record the following parameters daily in the eDiary from Visit 1 onwards:

- Morning peak expiratory flow (best of three), before rescue medication usage (L/min).
- Occasions of rescue usage over the previous 24-hours.
- Asthma symptom score over the previous 24-hours using a 6-point scale (Appendix 9).
- Frequency of awakening due to asthma symptoms requiring rescue medication use.

For safety the following alerts, indicative of worsening asthma, will be programmed into the eDiary with instructions to contact the investigator if any of the alert criteria are met. An alert in itself will not qualify as a clinically significant exacerbation:

- Decrease in morning PEF ≥30% on at least two of three successive days, compared with baseline (last 7 days of run-in).
- An increase of ≥50% in rescue medication on at least two of three successive days, compared with the average use for the previous week.
- Awakening due to asthma symptoms requiring rescue medication use for at least two of three successive nights.
- A symptom score of 5 for at least two of three successive days.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3) – where possible, these should be aligned with standard of care.

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Eyes, CV, Respiratory, Gastrointestinal and Neurological systems. Height (screening only) and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

- Temperature, pulse rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the resting state with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and should be taken before blood collection for laboratory tests.

8.3.3. Electrocardiograms (ECGs)

- Twelve-lead ECGs will be obtained at the time points specified in the SoA (see Section 1.3) using an ECG machine, provided by GSK via a designated central laboratory, that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- The QTcF formula must be used for *each* individual participant to determine eligibility. This formula may not be changed or substituted once the participant has been enrolled. Refer to Section 7.1.2 for the QTcF formula.
- If an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTcF values of the three ECGs to determine whether the participant should be screened/ randomised/ discontinued from the study intervention (but not from the study). Refer to Section 5.2 and Section 5.3.2 for exclusion/randomisation exclusion criteria related to ECG assessment and Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- ECG measurements will be made after the participant has rested in the supine position for 5 minutes. The ECG should be obtained after the vital signs assessments but before lung function testing followed by other study procedures. Collection shortly after a meal or during sleep should be avoided since QT prolongation can occur at these times.
- Paper ECG traces will be recorded at a standard paper speed of 25 mm/sec and gain of 10 mm/mV, with a lead II rhythm strip. There will be electronic capture and storage of the data by a validated method.
- Paper ECG traces are required to be maintained at the site with other source documents.

8.3.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and refer to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study until the Exit Visit (or Follow-up visit/call if applicable) should be repeated until the values return to normal or baseline or are

no longer considered significantly abnormal by the investigator or Medical Monitor. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the Sponsor notified.

- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- To maintain the treatment blind, the site and the central study team will not be sent information on haematology differential (absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes) from any visits post-randomisation.

8.3.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- A serum pregnancy test should be conducted for all WOCBP at the screening visit (Visit 1) and the Exit visit. In addition, a urine pregnancy test should be performed for all WOCBP prior to randomisation (Visit 2), on a monthly basis at the specified scheduled study visit, and at the Follow-up Visit/call (if applicable) as per the SoA (Section 1.3).
- A final urine pregnancy test should be conducted for all WOCBP, 30 weeks after the last administered dose of study intervention:
    - Participants who enter the OLE study will have a urine pregnancy test prior to receiving the first dose of open-label GSK3511294.
    - Participants who do not enter the OLE study should have a urine pregnancy test at the Follow-up Visit/call (Week 56). A self-reported home urine pregnancy test result is acceptable if the follow-up is conducted as a phone call visit.
    - Participants who withdraw early from the study should have a urine pregnancy test, 4 weeks after the WS Visit (see Section 7.2).
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Section 10.3. Asthma exacerbations should not be recorded in the AE section of the eCRF unless they meet the definition of a SAE.

The definitions of device-related safety events, (adverse device effects [ADEs] and serious adverse device effects [SADEs]), can be found in Section 10.7. Device deficiencies are covered in Section 10.7.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of intervention (Visit 2) until the Exit Visit or follow-up visit/call (if applicable) at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the Exit Visit or the follow-up visit/call (if applicable) at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions (in the eCRF) not as AEs.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to GSK within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify GSK.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 8.4.7), will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to GSK of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from GSK will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and GSK policy and forwarded to investigators as necessary.

8.4.5. Pregnancy

- Any female participant who becomes pregnant while participating in the study will not receive another dose of study intervention.
- Details of all pregnancies in female participants will be collected from the start of study intervention and until 30 weeks after the last administered dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within **24 hours** of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.4.6. Cardiovascular and Death Events

For any CV events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV CRF pages are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific CV section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF page is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.4.7. Adverse Events of Special Interest

Adverse events of special interest (AESI) include:

- Allergic reactions including anaphylaxis

  Note: these events will be assessed by the investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006] (Appendix 8).

- Type III hypersensitivity (immune complex disease/vasculitis) reactions
- Local injection site reactions
- QTc prolongation

See Section 2.3.1 for additional details.

8.4.8. Medical Device Deficiencies

Medical devices (PFS) are being provided for use in this study as a delivery method for GSK3511294 or matching placebo injections. To fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device Deficiency can be found in Section 10.7.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 10.3 of the protocol.

8.4.8.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- The method of documenting Medical Device Incidents is provided in Section 10.7.

8.4.8.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.8.3. Prompt Reporting of Medical Device Deficiencies to Sponsor

- Device deficiencies will be reported to the Sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.
- The Medical Device Deficiency Report Form will be sent to the Sponsor by email. If email is unavailable, then fax should be utilised.
- The Sponsor will be the contact for the receipt of device deficiency reports.

8.4.8.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all deficiencies occurring with any medical device provided for use in the study in order for the Sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.5. Pharmacokinetics

- Blood samples will be collected for measurement of plasma concentrations of GSK3511294 as specified in the SoA (Section 1.3).
- The actual date and time (24-hour clock time) of each sample will be recorded. Samples obtained at Visit 2 (Week 0) and Visit 10 (Week 26) should be drawn prior to dosing.
- Collection, processing, storage and shipping procedures are provided in the central laboratory manual.
- Intervention concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6. Genetics and Pharmacogenomics

China only: Genetic blood samples will not be collected from participants in China.

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Section 10.5 Genetics and Pharmacogenomics for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the central laboratory manual. Additional country specific requirements are specified in the SRM.

8.7. Biomarkers/ Pharmacodynamic Markers

8.7.1. Blood Eosinophil Counts

In order to investigate the PD effects of GSK3511294, blood eosinophil counts will be measured as part of the standard haematological assessments according to the SoA (Section 1.3). The site staff and central study team will be blinded to each participant's blood eosinophil count (as well as overall haematology differential [absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes]) from all post-randomisation blood tests. Total white blood cell counts will be available throughout the study.

8.7.2. Complement, IgE, and Inflammatory Markers

Blood samples will be collected to measure complement (C3 and C4) and total IgE, according to the SoA (Section 1.3).

A baseline serum sample will be collected at Visit 2 and stored. If necessary, this sample may be analysed for the presence of ANCA (using anti-MPO antibody and anti-PR3 antibody tests), and ANA, including anti-dsDNA antibodies. After dosing, additional inflammatory markers and tests may be considered on an ad-hoc basis should there be clinical concerns regarding an immune-mediated AE (see Section 7.5).

8.7.3. Exploratory Biomarkers

China only: Blood samples for exploratory biomarkers will not be collected from participants in China.

With the participant's consent and where permitted, a serum sample for exploratory biomarkers will be collected as specified in the SoA (Section 1.3). The samples will be stored after collection and may be analysed for any biomarkers that are thought to play a role in GSK3511294 response, asthma or related diseases, or to evaluate their association with observed clinical responses to GSK3511294. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to GSK3511294.

Participation in exploratory biomarker research is optional. Participants who do not wish to participate in the exploratory biomarker research may still participate in the study. Additional country specific requirements are specified in the SRM.

8.8. Immunogenicity Assessments

Antibodies to GSK3511294 will be evaluated in serum samples collected from participants according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the Exit Visit or the final in-clinic visit for participants who withdraw early from the study. Processing, storage and shipping procedures are provided in the SRM.

In the immunogenicity assessment for GSK3511294, a tiered analyses approach will use a validated binding ADA assay (screening, confirmation and titration assays) and a validated neutralisation antibody (NAb) assay. If necessary, further immune response characterisation may be performed as needed.

8.9. Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation data, associated with medical encounters, will be collected by the investigator and study-site personnel for all participants throughout the study. The data will be collected using a medical problems and healthcare utilisation worksheet according to the SoA (Section 1.3). Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to evaluate the effect of GSK3511294 on health care resource utilisation for asthma including hospitalisation, ED visits, and physician office/clinic visits.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary study objective is to test for the superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC, assessed by the annualised rate of clinically significant exacerbations measured over the study intervention period of 52 weeks.

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 and placebo.

9.2. Sample Size Determination

Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125).

9.2.1. Sample Size Assumptions

A sample size of 375 participants (2:1 GSK3511294 to placebo allocation ratio) is based on sufficient power to conclude superiority on primary and key secondary endpoints.

There is a possibility that greater than 375 participants will be randomised in the study due to local country requests or requirements, for example, the local competent authority specifying a minimum number to be enrolled.

9.2.1.1. Primary Endpoint

The assumed true annualised rate of exacerbations in the placebo arm is 1.18. Based on an assumed true treatment difference of a 50% reduction in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC, a sample size of 375 randomised participants (250 to GSK3511294, 125 to placebo) will provide 99% power for the primary endpoint at a 5% two-sided significance level [PASS, 2020].

The assumptions for the placebo rate and treatment effect are median values from an elicitation exercise which used Phase 3 anti-IL-5/5R historical data (~50% reduction in exacerbations) and expert opinion. The sample size is based also on an assumption of 0.8 for the dispersion parameter which was observed in two mepolizumab studies [Pavord, 2012; Ortega, 2014]. It was assumed that 14% of participant-years data will be missing due to study withdrawal, which is also consistent with mepolizumab studies.

Based on the assumptions above, the minimum observed treatment difference estimated to result in significance at the 5% two-sided significance level is a 27% reduction in exacerbations for GSK3511294 + SoC compared with placebo + SoC (rate ratio of 0.73).

9.2.1.2. Secondary Endpoints

Table 3 describes the assumptions and power values for two key secondary endpoints. The assumptions are obtained from the Phase 3 mepolizumab studies [Pavord, 2012; Ortega, 2014; Chupp, 2017].

Table 3 Power Calculations for Key Secondary Endpoints

Endpoint	Assumed treatment difference (GSK3511294 + SoC vs. placebo + SoC)	Standard deviation	Power
Change from baseline in SGRQ total score at Week 52	-7	17	96%
Change from baseline in ACQ-5 score at Week 52	-0.35	1.1	83%

9.2.2. Sample Size Sensitivity

The sample size and power calculations are based on assumptions about the true values for parameters. The power of the study is dependent on changes in these assumptions, in particular the assumed annualised exacerbation rates. Table 4 illustrates how changes in assumptions for two parameters (placebo + SoC annualised exacerbation rate and treatment effect) affect the power.

Table 4 Estimates of Power for Assumed Placebo + SoC Exacerbation Rate and Assumed Percent Reduction with GSK3511294 + SoC Compared with Placebo + SoC

Percent reduction in annualised exacerbation rate with GSK3511294 + SoC vs. placebo + SoC	Placebo + SoC annualised exacerbation rate			
	1.0	1.1	**1.18**	1.3
30%	61	63	65	67
40%	88	90	91	92
50%	98	99	**99**	99

9.2.3. Sample Size Re-estimation or Adjustment

There will be no sample size re-estimation.

9.3. Analysis Sets

For the purpose of analyses, the following populations are defined

Population	**Description**
Screened	All participants who sign the ICF.
Enrolled	All participants who entered the study. Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.
Randomised	All participants who were randomly assigned to study intervention in the study.
Full Analysis Set (FAS)	All randomised participants who receive at least one dose of study intervention. Participants will be analysed according to the intervention they are allocated at randomisation. This population will serve as the primary population for analyses of efficacy endpoints.
Safety	All randomised participants who receive at least one dose of study intervention. Participants will be analysed according to the intervention they are allocated at randomisation, unless a participant receives a different intervention to the randomised intervention at all protocol-defined administrations, in which case the participant will be analysed according to the actual intervention they received. This population will serve as the primary population for analyses of safety endpoints.

Further populations to be used for other assessments will be defined in the statistical analysis plan (SAP).

9.4. Statistical Analysis

The SAP will be finalised prior to un-blinding and it will include a more technical and detailed description of the statistical analyses described in this section.

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC.

9.4.2. Primary Endpoint

9.4.2.1. Main Estimand

Target Participant Population	Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.
Primary Endpoint	Annualised rate of clinically significant exacerbations over 52 weeks. Clinically significant exacerbations are defined in Section 8.2.2.
Intercurrent events and strategies	The anticipated key intercurrent events and corresponding strategies are: a) Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring b) Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred c) Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring
Summary measure	Ratio of the rates of exacerbations between GSK3511294 + SoC and placebo + SoC.
Analysis Method	The primary analysis of the annualised rate of clinically significant exacerbations will use a negative binomial model. Covariates included will be baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high dose, see Appendix 10), region, number of exacerbations in the year prior to the study, baseline % predicted FEV_1 and treatment group with $\log_e$(time in study in years) as an offset variable. The rate ratio and 95% confidence interval (CI) will be provided for the comparison between GSK3511294 + SoC and placebo + SoC.
Handling of missing data and intercurrent events leading to exclusion of data	Missing data or data excluded due to intercurrent events will be handled as follows: a) For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed “missing at random” (MAR) (based on all data included in the analysis under the current estimand strategy). b) For participants that withdraw from the study, preventing assessment of the primary endpoint, the data for the period following

	withdrawal will be assumed MAR (based on all data included in the analysis under the current estimand strategy). **Sensitivity analyses** will be conducted to investigate the conclusions from deviations from these assumptions regarding missing data for (b) above. Missing data for participants will be based on data from participants who have discontinued study intervention (off-treatment) but remained in the study [Roger, 2019]. A tipping point analysis will also be conducted that will impute missing data based on a plausible range of values for the rate of exacerbations per year. The imputed exacerbation rates will be varied independently for treatment arms. Further details will be provided in the SAP.

9.4.3. Secondary Endpoints

9.4.3.1. Main Estimands

Target Participant Population	Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.
Secondary Endpoints	• Change from baseline in SGRQ total score at Week 52 • Change from baseline in ACQ-5 score at Week 52 • Change from baseline in pre-bronchodilator FEV_1 at Week 52
Intercurrent events and strategies	The anticipated key intercurrent events and corresponding strategies: a) Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring. b) Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred. c) Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring
Summary measure	Difference in means between GSK3511294 + SoC and placebo + SoC.
Analysis Method	The analysis will be performed using a repeated measures mixed model. Covariates included will be baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high dose, see Appendix 10), number of exacerbations in the year prior to the study, baseline % predicted FEV_1,treatment group and visit, plus interaction terms for visit by baseline and visit by treatment group. The difference in means and 95% CI will be provided for the comparison between GSK3511294 + SoC and placebo + SoC.

Handling of missing data and intercurrent events leading to exclusion of data	Missing data or data excluded due to intercurrent events will be handled as follows: a) For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). b) For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy). **Sensitivity analyses** will be conducted to investigate the conclusions from deviations from these assumptions regarding missing and excluded data for (b) above. Missing data for participants will be based on data from participants who have discontinued study intervention (off-treatment) but remained in the study [Roger, 2019]. A tipping point analysis will also be conducted that will impute missing data based on a plausible range of means. The imputed means will be varied independently for treatment arms. Further details will be provided in the SAP.

The annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks will be evaluated using the same strategy as that described for the primary endpoint (see Section 9.4.2).

9.4.4. Other Endpoints

Full details of analysis methods to be used for other endpoints will be provided in the SAP.

9.4.5. Safety Analyses

All safety analyses will be performed on the Safety Population. Summaries of data will report data according to the nominal visit for which it was recorded. Occurrence of AEs, SAEs, AESIs, laboratory data, vital signs, and ECGs will be included in data displays in the form of listings, frequency tables, summary statistics, graphs, and statistical analyses where appropriate.

Adverse Events (AEs) will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and will be grouped by system organ class (SOC). AEs will be summarised by frequency and percentage of participants, by SOC and preferred term within each treatment group. Separate summaries will be presented for all AEs, drug-related AEs, serious AEs (SAEs), AEs leading to permanent discontinuation of study intervention or withdrawal from study and for any AEs of special interest.

9.5. Multiple Testing Strategy

The treatment comparison of interest for the primary and secondary endpoints is GSK3511294 100 mg SC + SoC vs placebo + SoC. A fixed sequence hierarchical testing procedure will be used to provide strong control of Type I error for multiplicity arising from the primary and multiple secondary endpoints. This will be carried out using a stepdown closed testing procedure where inference for an endpoint in the predefined hierarchy will be dependent on statistical significance having been achieved for the previous endpoints in the hierarchy. For example, for the primary endpoint, GSK3511294 + SoC will be compared to placebo + SoC at a two-sided 5% level. The next endpoint in the hierarchy (i.e. the first secondary endpoint) will be tested only if the test for the primary endpoint is significant at the two-sided 5% level. Testing will continue down the hierarchy for the remaining endpoints in an equivalent manner only if the previous endpoint in the hierarchy achieves statistical significance.

The hierarchy of the primary and secondary endpoints to be tested is as follows:

1. Annualised rate of clinically significant exacerbations over 52 weeks
2. Change from baseline in SGRQ at Week 52
3. Change from baseline in ACQ-5 at Week 52
4. Change from baseline in clinic pre-bronchodilator FEV_1 at Week 52
5. Annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

9.6. Interim Analysis

An unblinded interim analysis for futility will be performed by an statistical data analysis centre (SDAC) in conjunction with an IDMC to maintain study integrity. The futility analysis will not increase the type 1 error rate. Full details of the timing, operating characteristics and stopping boundary will be included in a statistical analysis plan and/or IDMC charter.

Blinded interim data will be used to complete a psychometric analysis (including assessment of reliability, validity and responsiveness) of the ADSD/ANSD and PROMIS fatigue items. This psychometric analysis will be performed when approximately 300 patients have 6 months data. This analysis is not expected to have any impact on the overall integrity of the study. No assessment of efficacy or safety will be included in this validation assessment.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide GSK with sufficient, accurate financial information as requested to allow GSK to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or their legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- For participants 12-17 years old, written informed assent must be obtained in addition to the legally authorised representative(s)' consent. Assent will be obtained in accordance with applicable country or IRB/Ethics Committee regulations. Written informed consent will be obtained from participants turning 18 years of age to continue participation in the study.
- The medical record must include a statement that written informed consent/assent was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorised person obtaining the informed consent/assent must also sign the ICF.
- Participants must be re-consented/re-assented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorised representative.

Participants who are rescreened are required to provide consent/assent and sign a new ICF/assent form.

GSK (alone or working with others) may use a participant’s coded study data and samples and other information to carry out this study; understand the results of this study; learn more about GSK3511294 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have GSK3511294 approved for medical use or approved for payment coverage.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by GSK. Any participant records or datasets that are transferred to GSK will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by GSK in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by GSK, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

An Independent Data Monitoring Committee (IDMC) comprised of clinical experts external to GSK will review unblinded data at defined timepoints during the study. If deemed appropriate by the IDMC, or upon request by GSK or investigators, additional timepoints for review may be added.

Details of the structure and function of the IDMC, and analysis plan for IDMC reviews, are outlined in the IDMC Charter, which is available upon request.

In addition to the IDMC, the GSK SRT will review blinded safety data at regular intervals throughout the study to ensure participant safety, which includes safety signal detection at any time during the study. Details of the SRT process will be available in relevant SRT documents. The SRT will inform the IDMC if any safety signals are identified.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymised participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymised patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- GSK or a designee is responsible for the data management of this study including quality checking of the data.
- GSK assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of GSK. No records may be transferred to another location or party without written notification to GSK.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- GSK will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, GSK will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

All protocol required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).

Local laboratory results may be required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation to be performed – for example: when results from screening Visit 1 should be available before dosing on Visit 2, or at any time when a participant is unwell and results are required urgently.

If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded in the CRF.

To maintain the blind, the following data for post-randomisation samples will not be reported to investigators and blinded Sponsor representatives: absolute and percentage values of eosinophils, neutrophils, lymphocytes, monocytes, and basophils.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

For China sites the urine specimen may be sent to the central laboratory for routine urinalysis instead of performing a local urine dipstick. Urinalysis should be performed at Visit 1 so that results are available before randomisation at Visit 2. Urine pregnancy test must still be performed at the site.

Table 5 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Haematology[1]	Platelet Count	*RBC Indices:*	*WBC count with Differential: (post-dose results blinded as described in footnote 1)*	
	RBC Count	MCV	WBC	
	Haemoglobin	MCH	Neutrophils	
	Haematocrit	%Reticulocytes	Lymphocytes	
			Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry[2]	BUN	Potassium	AST(SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase[3]	Albumin
		Magnesium	GGT	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination and UACR (if blood or protein is abnormal [evidence of microalbuminuria or haematuria of ≥1+])			
Pregnancy testing	• Highly sensitive serum pregnancy test at Screening Visit 1 and Exit Visit; urine pregnancy tests for all other scheduled visits (as needed for WOCBP)[4]			
Other Screening Tests	• FSH and oestradiol (if required to confirm postmenopausal status) • Parasitic Screening (only required in regions with high-risk or for participants who have visited high-risk regions in the past 6 months). Sites should use local laboratories. • Total IgE • Serum samples collected at baseline will be frozen and stored for later analyses, if necessary: anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			

NOTES:
ALT = Alanine Aminotransferase; ANA = anti-nuclear antibody; AST = Aspartate Aminotransferase; BUN = Blood urea nitrogen; FSH = Follicle-stimulating hormone; GGT= gamma glutamyl transferase, MPO=myeloperoxidase; PR3=proteinase 3; SGOT = Serum Glutamic-Oxaloacetic Transaminase; SGPT = Serum Glutamic-Pyruvic Transaminase; UACR = urinary albumin-creatinine ratio; WBC = white blood cell; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

1. To maintain the treatment blind, the following data for post-randomisation samples will not be reported to investigators and blinded Sponsor representatives: absolute and percentage values of eosinophils, neutrophils, lymphocytes, monocytes, and basophils.
2. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.6 All events of ALT ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalised ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported to GSK as an SAE.
3. If alkaline phosphatase is elevated, consider fractionating.
4. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalisation for signs/symptoms of the disease under study, death due to progression of disease, etc.).

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation • In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AE. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalised ratio (INR) >1.5 must be reported as SAE
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.

Assessment of Causality

- Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours and send/fax it to the Medical Monitor. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor or the SAE coordinator by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Medical monitor or the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.
- Permanent sterilisation methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.
   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female
   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   a) A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   b) Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance:

Female participants:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)c
• Bilateral tubal occlusion
• Azoospermic partner (vasectomised or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

• Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulationc
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulationc
  • oral
  • injectable

• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

Male participants: As GSK3511294 is a mAb that is not anticipated to interact directly with deoxyribonucleic acid (DNA) or other chromosomal material and minimal exposure through semen is expected, male participants will not be required to use contraception during the study.

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

China only: No genetic samples will be collected from participants in China.

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK3511294 or asthma with an eosinophilic phenotype and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3511294 or study interventions of this drug class, and indication. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- Additional analyses of DNA samples may be conducted if it is hypothesised that this may help further understand the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to GSK3511294 or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3511294 (or study interventions of this class) or asthma with an eosinophilic phenotype continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Required Actions, Monitoring and Follow-up Assessments

Liver Chemistry Stopping Criteria and Increased Monitoring Criteria are designed to assure participant safety and evaluate liver event aetiology.

Liver Chemistry Stopping criteria and Required Follow-up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 8xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
ALT ≥ 3xULN but <5xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks
ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions, Monitoring and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th>Follow-Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform follow-up assessments as described in the Follow-up Assessment column.
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5:</td><td>• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, within a week of meeting increased liver monitoring criteria.[5]
• Obtain a serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin.
• Fractionate bilirubin, if total bilirubin≥2xULN</td></tr>
</table>

Liver Chemistry Stopping Criteria	
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **For all other stopping criteria (total bilirubin <2xULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilise or return to within baseline **RESTART/RECHALLENGE** • **Do not restart/rechallenge** participant with study intervention since **it is not allowed per protocol;** continue participant in the study for any protocol specified follow-up assessments.	• Obtain complete blood count with differential to assess eosinophilia. This blood sample will be sent to the central laboratory to maintain the blind while study is ongoing. Results will be provided only if unblinding of a participant's treatment assignment is required. Also note that the mechanism of action of GSK3511294 leads to lowering of eosinophils. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications. • Record alcohol use on the liver event alcohol intake form **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease; complete Liver Imaging form

Liver Chemistry Stopping Criteria	
	• Liver biopsy may be considered and discussed with local specialist if available, for instance: ○ In patients when serology raises the possibility of autoimmune hepatitis (AIH) ○ In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention ○ In patients with acute or chronic atypical presentation: • If liver biopsy conducted complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3xULN and total bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5 which may indicate severe liver injury (possible 'Hy's Law'), **must be reported to GSK as an SAE**; the INR threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: hepatitis A Immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal, 2005].
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the central laboratory manual.

Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** total bilirubin <2xULN or INR≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** total bilirubin <2xULN or INR≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) until they resolve, stabilise or return to within baseline. • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, (total bilirubin <2xULN and INR ≤1.5) continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and total bilirubin <2xULN and INR ≤1.5, monitor participants twice monthly until liver chemistries resolve or return to within baseline.

References

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

10.7. Appendix 7: AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the Sponsor will comply with all local medical device reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.1.1 for the list of GSK medical devices).

10.7.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• An AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. • An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalisation. Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to foetal distress, foetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.7.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

10.7.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/device deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.7.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor or the SAE coordinator by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the Medical Monitor or the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

10.7.6. Reporting of SADEs

SADE Reporting to GSK
NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations. • Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

10.8. Appendix 8: Anaphylaxis Criteria

Joint National Institute of Allergy and Infectious Disease (NIAID)/ Food Allergy and Anaphylaxis Network (FAAN) Second Symposium on Anaphylaxis [Sampson, 2006]. The criteria do not make a distinction based on underlying mechanism. These criteria are summarised as follows:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalised hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
   a) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a) Involvement of the skin-mucosal tissue (e.g., generalised hives, itch-flush, swollen lips-tongue-uvula)
   b) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a) Adolescents (aged 12-17): low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

10.9. Appendix 9: Daily Asthma Symptom Score

Each morning, participants will record an asthma symptom score using the following scale:

Daily Symptom Score:

- 0 = No symptoms during the previous 24-hours.
- 1 = Symptoms for one short period during the previous 24-hours.
- 2 = Symptoms for two or more short periods during the previous 24-hours.
- 3 = Symptoms for most of the previous 24-hours which did not affect my normal daily activities.
- 4 = Symptoms for most of the previous 24-hours which did affect my normal daily activities.
- 5 = Symptoms so severe that I could not go to work/school or perform normal daily activities.

10.10. Appendix 10: Low, Medium and High Daily Doses of Inhaled Corticosteroids

Daily medium and high dose ICS options for adults and adolescents (12 years and older) are shown in Figure 1.

Figure 1 Low, medium and high daily doses of inhaled corticosteroids

Box 3-6. Low, medium and high daily doses of inhaled corticosteroids

This is not a table of equivalence, but instead, suggested total daily doses for the 'low', 'medium' and 'high' dose ICS options for adults/adolescents, p.54 and children 6–11 years, p.55, based on available studies and product information. Data on comparative potency are not readily available and therefore this table does NOT imply potency equivalence. Doses may be country-specific depending on local availability, regulatory labelling and clinical guidelines.

Low dose ICS provides most of the clinical benefit of ICS for most patients with asthma. However, ICS responsiveness varies between patients, so some patients may need **medium dose ICS** if their asthma is uncontrolled despite good adherence and correct technique with low dose ICS (with or without LABA). **High dose ICS** (in combination with LABA or separately) is needed by very few patients, and its long-term use is associated with an increased risk of local and systemic side-effects, which must be balanced against the potential benefits.

Adults and adolescents (12 years and older)			
Inhaled corticosteroid	**Total daily ICS dose (mcg) – see notes above**		
	Low	**Medium**	**High**
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (pMDI, extrafine particle*, HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle*, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	200		400
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400
Children 6–11 years – see notes above (for children 5 years and younger, see Box 6-6, p.153)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle*, HFA)	50-100	>100-200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80-160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50-100	>100-200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50-100	>100-200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; n.a. not applicable; pMDI: pressurized metered dose inhaler (non-chlorofluorocarbon formulations); ICS by pMDI should preferably be used with a spacer. *See product information.

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- The medium to high dose for Japanese adolescent subjects 15 years or younger will be ≥200 µg/day of FP or other ICSs of equivalent dose) as per the Japanese asthma pediatric guidelines.
- Updates as per GINA 2021:
- Beclometasone dipropionate (pMDI, extrafine particle, HFA) changed to Beclometasone dipropionate (**DPI or** pMDI, extrafine particle, HFA)
- Budesonide (DPI) changed to Budesonide (DPI, **or pMDI, standard particle, HFA**)
- Mometasone Furoate (DPI) Low, Medium and High total daily ICS doses **reference to product information as it depends on DPI device.**

10.11. Appendix 11: Recommended Measures Related to COVID-19 Pandemic

Overall Rationale for this Appendix:

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the study intervention or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the study intervention or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

STUDY PROCEDURES DURING COVID-19 PANDEMIC

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrolment and treatment decisions for trial participants.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants.

- Clinical investigators should document in site files and in participant notes/Electronic Heath Records as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).

- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

- Spirometry should not be conducted for participants with confirmed/suspected COVID-19.

Protocol Defined Procedures/Visits:

- Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, measurement of vital signs and weight, and preparation and administration of study drug (at the discretion of the investigator). It is the

responsibility of the investigator to inform GSK when this occurs and to document in source notes.

- Remote visits may be performed at the participant's home by qualified study personnel or at a local medical facility, unless the investigator deems that a site visit is necessary.
- Additional unscheduled safety assessments such as routine blood sampling may be performed at the discretion of the investigator including in the participant's home, if deemed necessary. Biological samples may be collected at a different location, other than the study site (e.g., at participant's home) by qualified study personnel or at a local medical facility according to standard operating procedures and applicable regulations (see note). Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If visits to a site/home are not feasible, then the medical evaluation of the participant's asthma may take place by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress. GSK will be accountable for working with the vendor to ensure the site has the required equipment, training and support for this model and should be notified as soon as possible by the investigator that the service is required.
- The study investigator is responsible for ensuring that the identification, management, and reporting of AEs and SAEs are completed in accordance with the protocol and applicable regulations. AEs are first reported by participants to the investigator/study team or may be identified by the study team during interactions with the participants via telemedicine encounters. In addition, mobile nurses may identify AEs as well and report them to the investigator for evaluation. Additionally, AEs may be identified from lab reports, imaging or ECG reports, and other records. As determined by the investigator, the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary.
- The participant should be informed of the plan and any potential risks associated with the virtual medium and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.
- The revised schedule of study activities is provided in Table 6.

Note: If the investigator wishes to conduct a trial visit at a location that has not been previously assessed by GSK, it is the investigator's responsibility to identify an adequate alternate location and to notify GSK of the alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, is well-equipped to perform study procedures and covered by an adequate insurance. Furthermore, the investigator should have sufficient oversight to ensure that the staff at the alternate location are trained to perform study procedures. Refer to and follow most recent local guidance and regulations if available or refer to FDA or EMA guidance available at time.

Study Intervention:

- If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (see Section 6 Study Intervention and Concomitant Therapy), a maximum dose interval of 28 weeks may be used.
- In-clinic visits are required for administration of the study intervention (Week 0 and Week 26).
- In some cases, trial participants who no longer have access to study intervention or the investigational site may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment).

Data Management/Monitoring:

- The medical problems and healthcare utilisation worksheet may be transmitted from and to the investigator by electronic mail and or conventional mail. If copies/scans of the paper worksheet are sent to the investigator by electronic mail, the participant should be instructed to maintain the original documents and to return them to the site when a visit to the site will be allowed.
- If the eDiary device was provided to the participant, it may be returned to the site by conventional mail after the end of the relevant data collection period (Visit 17 Exit Visit).
- If on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a patient and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.
- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilised during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK.

Assessments that can be Conducted Outside Clinical Study Site:

Activities/assessments that may be conducted outside of a clinical study site are indicated in Table 6.

- White boxes represent activities/assessments that are to be done during visits to the clinical study centre (pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 3, Visit 10, Visit 11 Exit Visit 17, and WS Visit if applicable).
- Grey boxes represent activities/assessments during study visits (Visits 4-9, Visits 12-16, and the FU Visit) that may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow (at the discretion of the investigator, based on safety and tolerability).
- The FU Visit may be conducted as a remote/home visit or as a phone call.
- During home visits, the scheduled collection of samples for laboratory and other assessments may be performed by a home healthcare professional.

Table 6 Schedule of Activities (SoA) Indicating Assessments that may be Conducted Outside of a Clinical Study Site

Protocol Activity	Pre-Screening	Screening/Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	**V0** [a]	**Visit 1** [a]	**V2**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
General Eligibility Assessments																					
Informed consent [a]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote a.
Genetic sample informed consent [d]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote d.
Demography data collections	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; All females must be assessed at Visit 1 to determine childbearing potential.
Inclusion/Exclusion criteria	X	X																			
Historical blood eosinophil count		X																			See footnote e.
Medical history		X																			Include cardiovascular (CV), CV risk factors, asthma, exacerbations, vasculitis, allergies and anaphylaxis.
Smoking status		X																			

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Parasite screening		X															X				Only required in regions with high-risk or for participants who have visited a high-risk region in the past 6 months. Use local laboratories for this test. For details refer to study reference manual (SRM).
eDiary registration and training		X																			Conduct thorough eDiary training at Screening Visit 1 and throughout the study on as-needed basis.
Randomisation criteria			X																		Assess prior to randomisation; see footnote e.
Efficacy Assessments																					
Review for exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Collection of exacerbations at Visit 1 is historical data.
Spirometry (pre- and post-bronchodilator FEV_1)[h]		X	X								X							X	X		FEV_1=Forced expiratory volume in 1 second; Spirometry should not be conducted for participants with confirmed/suspected COVID-19 (see Section 8.2.3).
ACQ-5			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		ACQ-5=Asthma Control Questionnaire-5

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0** [a]	**Visit 1** [a]	**V2**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Review eDiary (asthma symptoms, PEF summary)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PEF=Peak expiratory flow
HRQoL: PRO and Health Outcomes Assessments																					
SGRQ			X		X		X				X				X			X	X		SGRQ=St. George's Respiratory Questionnaire
PROMIS (fatigue items)			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PROMIS= Patient-reported outcomes measurement information system
SNOT-22			X								X							X	X		SNOT-22=Sino-nasal Outcomes Test-22 Questionnaire
Complete ADSD/ANSD		←========= daily =========→							X	X	X	X	X	X	X	X	X	X			ADSD/ANSD=Asthma Daily/Nightly Symptom Diary; To be completed daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.
Clinician-rated response to therapy							X				X				X			X	X		

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Patient-rated response to therapy							X				X				X			X	X		
PGI-S		X	X				X		X		X				X			X	X		PGI-S: Patient Global Impression of Severity (of asthma)
PGI-C							X		X		X				X			X	X		PGI-C: Patient Global Impression of Change (from baseline of asthma severity)
Safety Assessments																					
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Ensure maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications are reviewed.
Physical Examination		X																X	X		Include height and weight for the complete physical exam at Screening Visit 1. Height can be omitted for subsequent visits.
Vital Signs		X	X			X			X		X	X			X		X	X	X		

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
12-lead ECG		X	X	X							X	X						X	X		ECG must be performed and assessed pre-dose. Twelve-lead ECG central over-read values should be used at all visits with the exception of Visit 2 and Visit 10 where 12-lead ECG machine read values should be used.
AE/SAE Assessment	X [g]	X [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE=Adverse events; SAE=Serious adverse events; see footnote g.
Laboratory Assessments																					
Haematology with white blood cells count [f]		X [e]	X	X	X	X	X		X		X	X	X		X		X	X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing; see footnotes e and f.
Total IgE			X																		
Clinical Chemistry		X	X		X	X	X		X		X	X			X		X	X	X		Include liver chemistry.
Pregnancy Test (WOCBP only)		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	Serum pregnancy test should be done at screening Visit 1 and Exit Visit/ Withdraw from study visit; urine pregnancy tests should be done for all other assessments; WOCBP=Women of childbearing potential; See Section 8.3.5 for additional information.

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Urinalysis		X	(X)								X							X	X		Conduct at Visit 2 if not completed at Visit 1. Note: dipstick, send for analysis if abnormality is identified by dipstick **China Only:** For China sites the urine specimen may be sent to the central laboratory for routine urinalysis instead of performing a local urine dipstick. Urinalysis should be performed at Visit 1 so that results are available before randomisation at Visit 2. Urine pregnancy test must still be performed at the site.
Anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			X																		ANA=antinuclear antibodies; MPO=myeloperoxidase; PR3=proteinase 3. Collected baseline sample will be stored and may be tested if necessary (see Section 7.5).
Complement C3 and C4			X				X				X				X			X	X		
PK sample			X	X	X	X	X		X		X	X	X		X			X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing.

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Immunogenicity sample			X	X	X	X	X				X	X	X	X	X			X	X		
Blood biomarker sample			X				X				X				X			X			Sample will be stored and may be analysed for exploratory biomarkers (see Section 8.7.3) **China only:** Blood samples for exploratory biomarkers will not be collected from participants in China.
Genetics sample			←========== The genetics sample can be collected at Visit 2 or any visit after ==========→																		See footnote d.
Study intervention																					
Administer study intervention			X								X										Study intervention will only be administered in the clinic. Any scheduled assessments or sample draws should be performed beforehand. Monitor participant for at least 2h after administration (see Section 6.5).
eCRF/worksheets/other																					
Dispense Rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Register Visit in the IRT system		X	X								X								X		IRT=interactive response technology
Provide worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				The worksheet is a medical problems and healthcare utilisation worksheet.
Review worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
eDiary close out																		X	X		
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		eCRF=electronic Case Report Form

a. Informed Consent must be obtained prior to initiating any study assessments. Pre-screening Visit 0 can occur any time from 0 to 14 days before Screening Visit 1.
b. Randomisation Visit 2 is 1 week after Screening Visit 1 but can be extended to up to 6 weeks after Visit 1 if, for example, a participant has an exacerbation during the run-in period. Results from Screening Visit 1 procedures must be available for review of randomisation criteria.
c. If a participant withdraws from the study, then the Withdraw from Study (WS) Visit should be conducted 26 weeks after the last administered dose of study intervention, i.e., at Week 26 if the second dose of study intervention was not received, or at Week 52 if the second dose of study intervention was received. A follow-up visit/call should also be conducted 30 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing.
d. Informed Consent for optional genetics research must be obtained before collecting a sample. **China only:** Genetic Informed Consent will not be collected from participants in China. Genetic blood samples will not be collected from participants in China.
e. To be randomised, participants without a historical blood eosinophil count of ≥300 cells/µL in the 12 months prior to Screening Visit 1, must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. If the Screening Visit test result does not meet the blood eosinophil count eligibility criteria, the laboratory assessment may be repeated, at the discretion of the investigator, if it is judged to be likely in the eligible range for study inclusion within the run-in period prior to Visit 2.
f. For haematology samples collected after Randomisation, the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will not be reported to site staff and Sponsor (to maintain the treatment blind). However, sites will be sent total white blood counts throughout the study. Samples should be taken prior to dosing at Week 0 and Week 26 visits.

g. SAEs must be collected from signing of Informed Consent if considered related to study procedures.
h. If a patient fails the protocol-specified reversibility criterion or FEV_1 inclusion criteria, spirometry retest is allowed during the run-in period.

10.12. Appendix 12: Country-specific requirements

Participants in China will not participate in the genetics (Appendix 5) or exploratory biomarker (Section 8.7.3) research.

10.13. Appendix 13: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine transaminase
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibody
ADE	Adverse device events
ADSD	Asthma Daily Symptom Diary
ANSD	Asthma Nightly Symptom Diary
Anti-HBc	Hepatitis B core antibody
Anti-IL-5	Anti-Interleukin-5
Anti-IL-5R	Anti-Interleukin-5 receptor
AST	Aspartate aminotransferase
BiPAP	Bilevel positive airway pressure
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
cm	Centimetre
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous positive airway pressure
CPK	Creatine phosphokinase
CRF	Case report form
CS	Corticosteroid
CSR	Clinical study report
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
ECG	Electrocardiogram
ED	Emergency department
eDiary	Electronic diary
EDTA	Ethylenediaminetetraacetic acid or disodium edetate
EGPA	Eosinophilic granulomatosis with polyangiitis
FAAN	Food Allergy and Anaphylaxis Network
FAS	Full Analysis Set
FEV_1	Forced expiratory volume in 1 second
FP	Fluticasone propionate
FSH	Follicle stimulating hormone
FTIH	First Time in Humans

FVC	Forced vital capacity
g	Grams
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma glutamyl transferase
GINA	Global Initiative for Asthma
GLDH	Glutamate dehydrogenase
GSK	GlaxoSmithKline
h	Hours
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HFA	Hydrofluoroalkane product
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IFU	Instruction for use
Ig	Immunoglobulin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IM	Intramuscular
IMP	Investigational medicinal product
INR	International normalised ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
kg	kilogram
L	Litre
LA	Long-acting
LABA	Long-acting β-agonist
LAM	Lactational amenorrhea method
LAMA	Long-acting muscarinic antagonist
LDH	Lactate dehydrogenase
LTRA	Leukotriene receptor antagonist
mAb	Monoclonal antibody
MAR	Missing at random

mcg (μg)	Microgram
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Millilitres
mm Hg	Millimetre of mercury
mol	Mole
MPO	myeloperoxidase
MSDS	Material Safety Data Sheet
msec	Milliseconds
NAb	Neutralising antibody
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NIMP	Non-investigational medicinal product
OCS	Oral corticosteroid
OLE	Open-label extension
PC_{20}	Provocative concentration causing a 20% fall in FEV_1
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PD_{20}	Provocative dose that decreases FEV_1 by 20%
PEF	Peak expiratory flow
PFS	Pre-filled safety syringe
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PR3	Proteinase 3
PRO	Patient-reported outcomes
PROMIS	Patient-reported outcomes measurement information system
QTcF	QTc corrected by Fridericia's formula
QTL	Quality tolerance limits
R&D	Research and Development
RNA	Ribonucleic acid
RBC	Red blood cell
SABA	Short-acting β-agonist
SADE	Serious adverse device event
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SDAC	Statistical data analysis centre
SGPT	Serum glutamic pyruvic transaminase
SGOT	Serum glutamic oxaloacetic transaminase
SGRQ	St. George's Respiratory Questionnaire
SNOT	Sino-nasal Outcomes Test

SoA	Schedule of assessments
SoC	Standard of care
SOC	System organ class
SRM	Study Reference Manual
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
UACR	Urinary albumin-creatinine ratio
UK	United Kingdom
ULN	Upper Limit of Normal
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential
w/v	Weight/volume
µL	Microlitre

Trademark Information

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10.14. Appendix 14: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

10.14.1. Amendment 1: 17-Aug-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment: Amendment 01 is a global amendment to include modifications based on regulatory suggestion and additional changes were incorporated which align with program revisions and/or updates as listed in table below.

Section # and Name	Description of Change	Brief Rationale
Title page, Section 1.1 Synopsis and Section 2.1 Study Rationale	Addition of name “depemokimab”	To update the protocol with the recently approved generic name of GSK3511294
Section 1.3 Schedule of Activities and Table 6 of Appendix 11	Term “Demography and childbearing status” modified to “Demography data collection” Added text “Collection of exacerbations at Visit 1 is historical data” Term “Haematology with differential” modified to “Haematology with white blood cell count”. Added text to clarify that details regarding parasite screening are mentioned in study reference manual	Minor modification for more clarity
	Text “-56 to -7” modified to “-56 to -42”, “Week -8 to –1” modified to “Week -8 to -6”	Clarification
	Inclusion of an ECG at week 2 and week 28	Revision to address request of health authority
	Only screening, randomization, dispensing and withdrawal visits need interactive response technology (IRT), hence corrections	Visits which require IRT registration were clarified

Section # and Name	Description of Change	Brief Rationale
	made accordingly	
	Added Parasitic screening at week 48 Added a clinical chemistry visit at week 48	Modification with respect to the planned open label extension study
Section 1.1 Synopsis, Section 4.1 Overall design and Appendix 11	Added Visits 3 and 11 as in-person clinic visits.	Due to the inclusion of an ECG at week 2 and week 28 these visits can not be conducted remotely or virtually.
Section 4.1.1 Study Phases, Duration and Treatment Arms (Table 1)	Term “Clinic” modified to “Study”	Clarification
Section 5.1 Inclusion Criteria	Added text in inclusion criteria related to pregnancy	Clarification
Section 5.2 Exclusion Criteria	Exclusion of participants with allergy/intolerance to the excipients of GSK3511294 in Section 6.1	Updated wording for more clarity for study intervention and its excipients
Section 5.3.1 Randomization Inclusion Criteria	Airway reversibility or Airway hyperresponsiveness documented in the 24 months prior to Visit 2 instead of previous 12 months	To provide flexibility for enrolling participants that have demonstrated airway reversibility/hyperresponsiveness
Section 5.3.2 Randomization Exclusion Criteria	Revised QTc criteria	Revised wording for clarification
Section 6.9.1 Permitted Medications and Non-Drug Therapies	Text added for permission to receive COVID-19 Vaccine	Clarification considering the COVID-19 pandemic situation
Section 6.9.2 Prohibited Medications and Non-Drug Therapies	Removed “troleandomycin” from prohibited medication	As per the program level updated troleandomycin is no longer a prohibited medication
Section 6.9.3. Rescue Medicine	Low dose ICS/LABA is not permitted as rescue medication. Rescue medication usage will be recorded in the eDiary.	Revised wording for providing more clarity
Section 8.1.1 Pre-screening Visit (Visit 0)	Only screening (Visit 1), randomization (Visit 2), dispensing (Visit 10) and withdrawal visits need IRT, hence corrections made accordingly	Visits which require IRT registration were clarified
Section 8.2.2 Asthma	Text deleted “Additional details on	Text removed to align with the

Section # and Name	Description of Change	Brief Rationale
Exacerbations	the process for determination of clinically significant exacerbations can be found in the SAP".	Statistical Analysis Plan
8.2.3.1. Reversibility using the Maximum Post-Bronchodilator Method	Current "The procedures involved in the Maximum Post-Bronchodilator Method are those generated by the **Pulmonary Physiology Subcommittee** " Previously "The procedures involved in the Maximum Post-Bronchodilator Method are those generated by the and not by *Asthma Clinical Research Network"* Current "Details of reversibility procedure mentioned in **SRM**" Previously "Details of reversibility procedure mentioned in in *third party vendor manual*"	Clarification
Section 8.2.4. St. George's Respiratory Questionnaire (SGRQ)	The SGRQ will contain 50 items instead of previous 51.	Clarification
Section 8.2.8. Patient Global Impression of Asthma Severity/Change (PGI-S, PGI-C), Section 8.2.10. Asthma Daily Symptom Diary/Asthma Nightly Symptom Diary (ADSD/ANSD)	Questionnaire only be administered to participants for whom an appropriate translation is available	Clarification
Section 8.2.10. Asthma Daily Symptom Diary/Asthma Nightly Symptom Diary (ADSD/ANSD)	Updated the information regarding use of ADSD and ANSD	Correction of the timeframe for completing daily symptom diary
Section 8.3.2 Vital Signs	Text "Oral or skin Temperature" modified to "Temperature"	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 8.6 Genetics and Pharmacogenomics, Section 8.7.3. Exploratory Biomarkers	Clarified that country specific requirements regarding genetic and biomarker samples will be mentioned in SRM	Country specific requirements will be specified in the SRM
Section 9.3 Analysis sets	mITT description updated, Safety Population deleted	Revised description of mITT population to provide clarification that mITT population will be used as primary population for some other endpoints apart from efficacy.
	Clarification of analysis populations which will be defined in SAP.	Clarification
Appendix 2 Clinical Laboratory Tests	Added gamma glutamyl transferase to the table of protocol-required clinical laboratory test parameters.	Added to align with clinical laboratory worksheet.
Section 10.3.2 Definition of SAE	Modified definition of SAE	Revised as per the latest definition of SAE.
Section 10.3.5 Reporting of SAE to GSK	Removed the requirement of SAE reporting in eCRF within 72 hours	Removal of additional step of eCRF check.
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

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TITLE PAGE

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Protocol Number: 213744

Compound Number or Name: GSK3511294

Brief Title: Placebo-controlled efficacy and safety study of GSK3511294 in participants with severe asthma with an eosinophilic phenotype

Study Phase: Phase 3A

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
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Manufacturer: GlaxoSmithKline

Regulatory Agency Identifying Number(s):

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SPONSOR SIGNATORY:

Jonathan Steinfeld Sr. Clinical Development Director	Date

Medical Monitor Name and Contact Information can be found in the Study Reference Manual (SRM).

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Brief Title: Placebo-controlled efficacy and safety study of GSK3511294 in participants with severe asthma with an eosinophilic phenotype

Rationale:

GSK3511294 is being developed as a long-acting (LA) subcutaneous (SC) injectable anti-interleukin-5 (anti-IL-5) therapy and is expected to deliver an efficacy and safety profile similar to current anti-IL-5 therapies with a reduced dosing frequency (once every 26 weeks). The aim of this study is to investigate the efficacy and safety, over a 52-week treatment period, of GSK3511294 100 mg SC given once every 26 weeks as adjunctive therapy in participants with uncontrolled severe asthma with an eosinophilic phenotype.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

Overall Design:

This study employs a multi-centre, randomised, placebo-controlled, double-blind, parallel group design to assess the efficacy and safety of GSK3511294 in participants with severe uncontrolled asthma with an eosinophilic phenotype despite standard of care (SoC) treatment with medium to high dose inhaled corticosteroid (ICS) plus at least one additional controller. All participants will receive study intervention as an adjunct therapy while remaining on their existing asthma therapy throughout the study.

Brief Summary:

The purpose of this study is to assess the efficacy and safety of GSK3511294 as an adjunctive therapy in participants with severe uncontrolled asthma with an eosinophilic phenotype. During the 52-week treatment period, participants will receive two doses (at Week 0 and Week 26) of add-on study intervention (GSK3511294 100 mg or matching placebo) by SC injection, while remaining on their existing maintenance asthma therapy (that excludes biologics) throughout the study. Assessments will include the annualised rate of clinically significant exacerbations and measures of lung function, asthma control, and safety.

Number of Participants:

Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125).

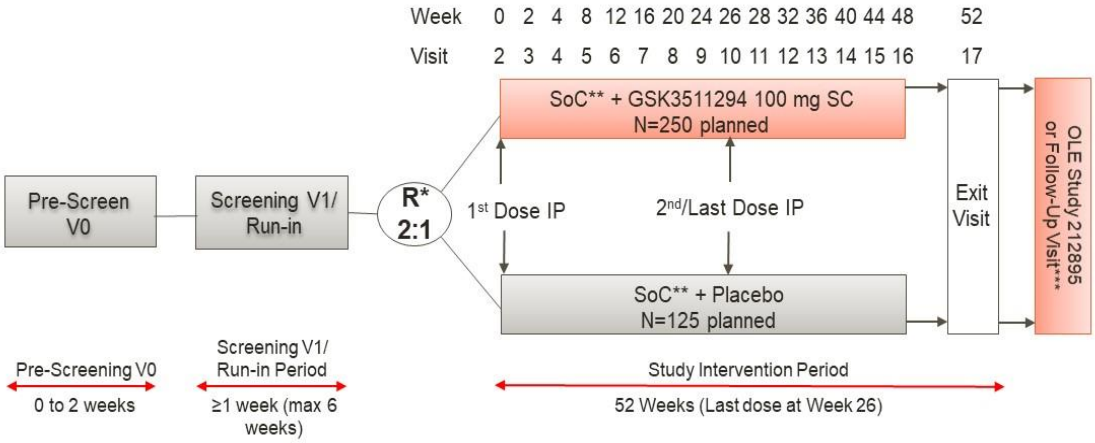
Intervention Groups and Duration:

The study will consist of a pre-screen period (0-2 weeks), a run-in period (1-6 weeks), and a study intervention period (52 weeks). After the run-in period, participants will be randomised in a 2:1 ratio using an interactive response technology (IRT) system in a blinded manner to receive either GSK3511294 100 mg or placebo by SC injection. Randomisation will be stratified based on baseline ICS dose (medium or high dose). Two doses of study intervention will be administered in the clinic: the first at randomisation Visit 2 (Week 0) and the second at Visit 10 (Week 26). Participants will be assessed at each scheduled visit (a total of 17 study visits) during the 52-week treatment phase. Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 10, Exit Visit 17, and WS Visit (if applicable).

Participants who receive both doses of study intervention and complete the Exit Visit will be eligible to participate in an open-label extension (OLE) study (Study 212895), during which they will receive two doses of open-label GSK3511294 100 mg SC over another 52 weeks. Participants who do not enter the OLE study will have a follow-up visit/call at Week 56.

Independent Data Monitoring Committee: Yes

1.2. Schema



** R = Randomisation: To be randomised participants without a historical blood eosinophil count of ≥300 cells/µL must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. Participants will remain on their standard of care (SoC) asthma therapy throughout the intervention period and will be randomised 2:1 to receive GSK3511294 (100 mg) or placebo.*

*** SoC = medium to high dose ICS (≥440 µg FP HFA daily or clinical comparability) plus additional controller. SoC asthma therapy to exclude biologics.*

**** OLE = Open label extension. Willing participants will continue directly into OLE Study 212895. Participants unwilling to continue will have a follow-up visit 4 weeks after the Exit Visit.*

1.3. Schedule of Activities (SoA)

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
General Eligibility Assessments																					
Informed consent [a]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote a.
Genetic sample informed consent [d]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote d.
Demography and childbearing status	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; All females must be assessed at Visit 1 to determine childbearing potential.
Inclusion/Exclusion criteria	X	X																			
Historical blood eosinophil count		X																			See footnote e.
Medical history		X																			Include cardiovascular (CV), CV risk factors, asthma, exacerbations, vasculitis, allergies and anaphylaxis.
Smoking status		X																			
Parasite screening		X																			Only required in regions with high-risk or for participants who have visited a high-risk region in the past 6 months. Use local laboratories for this test.
eDiary registration and training		X																			Conduct thorough eDiary training at Screening Visit 1 and throughout the study on as-needed basis.
Randomisation criteria			X																		Assess prior to randomisation; see footnote e.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Efficacy Assessments																					
Review for exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spirometry (pre- and post-bronchodilator FEV_1)		X	X								X							X	X		FEV_1=Forced expiratory volume in 1 second; Spirometry should not be conducted for participants with confirmed/suspected COVID-19 (see Section 8.2.3).
ACQ-5			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		ACQ-5=Asthma Control Questionnaire-5
Review eDiary (asthma symptoms, PEF summary)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PEF=Peak expiratory flow
HRQoL: PRO and Health Outcomes Assessments																					
SGRQ			X		X		X				X				X			X	X		SGRQ=St. George's Respiratory Questionnaire
PROMIS (fatigue items)			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PROMIS= Patient-reported outcomes measurement information system
SNOT-22			X								X							X	X		SNOT-22=Sino-nasal Outcomes Test-22 Questionnaire
Complete ADSD/ANSD		←========= daily =========→							X	X	X	X	X	X	X	X	X	X			ADSD/ANSD=Asthma Daily/Nightly Symptom Diary; To be completed daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.
Clinician-rated response to therapy							X				X				X			X	X		
Patient-rated response to therapy							X				X				X			X	X		

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0** [a]	**Visit 1** [a]	**V2**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
PGI-S		X	X				X		X		X				X			X	X		PGI-S: Patient Global Impression of Severity (of asthma)
PGI-C							X		X		X				X			X	X		PGI-C: Patient Global Impression of Change (from baseline of asthma severity)
Safety Assessments																					
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Ensure maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications are reviewed.
Physical Examination		X																X	X		Include height and weight for the complete physical exam at Screening Visit 1. Height can be omitted for subsequent visits.
Vital Signs		X	X			X			X		X	X			X		X	X	X		
12-lead ECG		X	X								X							X	X		
AE/SAE Assessment	X [g]	X [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE=Adverse events; SAE=Serious adverse events; see footnote g.
Laboratory Assessments																					
Haematology with differential [f]		X [e]	X	X	X	X	X		X		X	X	X		X		X	X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing; see footnotes e and f.
Total IgE			X																		
Clinical Chemistry		X	X		X	X	X		X		X	X			X			X	X		Include liver chemistry.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Pregnancy Test (WOCBP only)		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	Serum pregnancy test should be done at screening Visit 1 and Exit Visit; urine pregnancy tests should be done for all other assessments; WOCBP=Women of childbearing potential; See Section 8.3.5 for additional information.
Urinalysis		X	(X)								X							X	X		Conduct at Visit 2 if not completed at Visit 1. Note: dipstick, send for analysis if abnormality is identified by dipstick
Anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			X																		ANA=antinuclear antibodies; MPO=myeloperoxidase; PR3=proteinase 3. Collected baseline sample will be stored and may be tested if necessary (see Section 7.5).
Complement C3 and C4			X				X				X				X			X	X		
PK sample			X	X	X	X	X		X		X	X	X		X			X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing.
Immunogenicity sample			X	X	X	X	X				X	X	X	X	X			X	X		
Blood biomarker sample			X				X				X				X			X			Sample will be stored and may be analysed for exploratory biomarkers (see Section 8.7.3)
Genetics sample			←========== The genetics sample can be collected at Visit 2 or any visit after ==========→																		See footnote d.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Study intervention																					
Administer study intervention			X								X										Study intervention will only be administered in the clinic. Any scheduled assessments or sample draws should be performed beforehand. Monitor participant for at least 2h after administration (see Section 6.5).
eCRF/worksheets/other																					
Dispense Rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Register Visit in the IRT system	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	IRT=interactive response technology
Provide worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				The worksheet is a medical problems and healthcare utilisation worksheet.
Review worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
eDiary close out																		X	X		
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		eCRF=electronic Case Report Form

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	

a. Informed Consent must be obtained prior to initiating any study assessments. Pre-screening Visit 0 can occur any time from 0 to 14 days before Screening Visit 1.

b. Randomisation Visit 2 is 1 week after Screening Visit 1 but can be extended to up to 6 weeks after Visit 1 if, for example, a participant has an exacerbation during the run-in period. Results from Screening Visit 1 procedures must be available for review of randomisation criteria.

c. If a participant withdraws from the study, then the Withdraw from Study (WS) Visit should be conducted 26 weeks after the last administered dose of study intervention, i.e., at Week 26 if the second dose of study intervention was not received, or at Week 52 if the second dose of study intervention was received. A follow-up visit/call should also be conducted 30 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing.

d. Informed Consent for optional genetics research must be obtained before collecting a sample.

e. To be randomised, participants without a historical blood eosinophil count of ≥300 cells/µL in the 12 months prior to Screening Visit 1, must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1.

f. For haematology samples collected after Randomisation, the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will not be reported to site staff and Sponsor (to maintain the treatment blind). However, sites will be sent total white blood counts throughout the study. Samples should be taken prior to dosing at Week 0 and Week 26 visits.

g. SAEs must be collected from signing of Informed Consent if considered related to study procedures.

2. INTRODUCTION

2.1. Study Rationale

Anti-IL-5 therapies have an established efficacy and long-term safety profile and are a cornerstone of severe asthma management for patients with an eosinophilic phenotype [GINA, 2020]. Three antagonists of IL-5 (mepolizumab and reslizumab) or its receptor (IL-5R) (benralizumab) are approved for severe asthma with an eosinophilic phenotype, as an add-on treatment administered every 4 to 8 weeks.

GSK3511294 is being developed as a LA SC injectable anti-IL-5 therapy and is anticipated to deliver an efficacy and safety profile similar to current anti-IL-5 therapies with a reduced dosing frequency (once every 26 weeks). The aim of this study is to investigate the efficacy and safety, over a 52-week treatment period, of GSK3511294 100 mg SC given once every 26 weeks as adjunctive therapy to participants with uncontrolled severe asthma with an eosinophilic phenotype.

2.2. Background

Persistent eosinophil inflammation is a feature of more than 50% of patients with severe asthma [Chung, 2014]. Several monoclonal antibodies (mAbs) targeting eosinophil inflammation have received marketing authorisation for asthma with an eosinophilic phenotype, including 3 targeting either interleukin-5 (IL-5) or its receptor (IL-5R): mepolizumab (Nucala), reslizumab (Cinqair/Cinqaero), and benralizumab (Fasenra). All three, by utilising blood eosinophils as a biomarker to predict patients likely to respond to therapy, have been shown to reduce asthma exacerbations, and improve lung function and health-related quality of life (HRQoL), in patients with asthma with an eosinophilic phenotype [Haldar, 2009; Castro, 2011; Pavord, 2012; Bel, 2014; Ortega, 2014; Castro, 2015; Bleecker, 2016; FitzGerald, 2016; Chupp, 2017].

Evidence supporting the tolerability of targeting IL-5/5R is provided by long-term extension studies for mepolizumab [Lugogo, 2016; Khatri, 2019; Khurana, 2019], reslizumab [Murphy, 2017], and benralizumab [Busse, 2019] as well as efficacy data in real-world evidence settings for mepolizumab [Harrison, 2020; Bagnasco, 2019; Pertzov, 2019; Schleich, 2020]. Clinical trial data over more than 10 years combined with real-world evidence, have demonstrated that treatments targeting the IL-5 pathway are both highly effective and well-tolerated. Based on this established efficacy and safety, anti-IL-5/5R therapies are now a cornerstone of severe asthma management and are endorsed by international guidelines for appropriate patients that continue to exacerbate despite optimised care with Step 4 or Step 5 treatment (medium and high dose ICS) [GINA, 2020].

GSK3511294 is a humanised, affinity matured mAb that blocks human IL-5 binding to its receptor and belongs to the established class of anti-IL-5 therapies for severe asthma management. Compared with mepolizumab, GSK3511294 contains 7 amino acid substitutions to the heavy chain sequence: 4 amino acid changes introduced in the heavy chain variable region and 3 amino acid changes (YTE) in the Fc region. The resulting antibody has increased affinity and half-life. Evidence to date indicate that these amino

acid changes extend the pharmacokinetics (PK) and pharmacology of GSK3511294 to enable less frequent dosing with an anticipated similar efficacy and safety profile relative to mepolizumab (administered chronically).

Long-acting alternatives that can be administered on a less frequent basis are recognised as successful approaches for chronic indications. As a LA anti-IL-5 therapy, GSK3511294 is anticipated to have an efficacy and safety profile that is similar to those of the currently-approved therapies in its class, but with a single administration every 26 weeks, as opposed to the current regimen of every 4 weeks for mepolizumab and reslizumab, or every 8 weeks for benralizumab (every 4 weeks for the first 3 doses).

A detailed description of the chemistry, pharmacology, and safety of GSK3511294 is provided in the current Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2016N295843_03 or later].

2.3. Benefit: Risk Assessment

Summaries of findings from non-clinical studies conducted with GSK3511294 and completed FTIH study 205722 can be found in the current IB [GlaxoSmithKline Document Number 2016N295843_03 or later]. The following section outlines the risk assessment and mitigation strategy for this protocol:

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention GSK3511294		
• Allergic reactions including anaphylaxis.	• Allergic reactions with the most severe form being anaphylaxis (see Appendix 8), are potential risks associated with mAbs. • No allergic reactions or anaphylaxis have been reported with GSK3511294 in FTIH study 205722 in participants with mild to moderate asthma. One participant reported an event under Hypersensitivity SMQ with preferred term of rash verbatim "localised rash both bends of arms", 82 days post 30 mg SC dose of GSK3511294. The event was non-serious, of mild intensity, resolved within 10 days and was considered unrelated to the study intervention by the investigator.	• Daily monitoring of serious adverse events (SAEs) by Medical Monitor/SAE coordinator; regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GSK safety review team. • Use of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 8). • Participants will be monitored in clinic for immediate hypersensitivity and any other untoward effects for a minimum of 2 hours post-injection (both at randomisation and at Week 26). In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study intervention, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care if appropriate. • An independent data monitoring committee (IDMC) will review unblinded safety data at regular intervals.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Participants with severe allergic reaction/anaphylaxis with no alternative explanation after the first dose will not receive another dose.
• Type III Hypersensitivity (Immune complex disease/vasculitis)	• Adverse effects of vascular inflammation consistent with immune complex disease were observed in 1 female monkey in the 1-month toxicity study after administration of 10 mg/kg. A further monkey had a minimal focal inflammation after administration of 100 mg/kg. Immune complex disease was not observed in the 6-month repeat dose (2 doses) study at the same doses. It is unknown if this will translate to humans as preclinical models are not necessarily predictive of clinical findings in humans. • No AEs of Type III hypersensitivity have been reported with GSK3511294 in FTIH study 205722 in participants with mild to moderate asthma (36 participants received GSK3511294; 12 participants received placebo).	• Participants with current diagnosis of vasculitis will be excluded. Participants with high clinical suspicion of vasculitis at screening will be evaluated and excluded from enrolment if diagnosed (Section 5.2). • Daily monitoring of SAEs will be done by Medical Monitor/SAE coordinator; regular systematic review of adverse event (AE)/SAE data from ongoing studies will be performed by a GSK safety review team. • IDMC will review unblinded safety data at regular intervals; any events suggestive of immune complex disease will be reviewed by a rheumatologist (member of the IDMC). • Protocol guidance on early identification of vasculitis events is provided (see Section 7.5). • Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation after the first dose will not receive another dose of study intervention (see Section 7.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• Immunogenicity, anti-drug antibodies (ADAs)	• Biopharmaceutical products may elicit ADAs and neutralising antibodies (NAb), which have the potential to modulate PK or pharmacodynamics (PD), or to produce adverse reactions. • In FTIH study 205722, none of the participants tested positive for ADA at baseline. Overall, 9 participants (25%) had confirmed positive results for ADA at any time post-baseline, primarily in the GSK3511294 30 mg dose group (5 participants), which was also the group with the highest total serum IL-5 concentrations. This apparent correlation warrants further investigation. There were no major differences observed in the GSK3511294 plasma concentration-time and blood eosinophil count-time profiles as well as AE reporting between ADA-positive and ADA-negative participants. Neutralising antibodies were not tested in this study.	• Blood samples will be collected for detection of both ADA and NAb (see Section 8.8).
• Local injection site reactions	• A potential risk of any drug delivered via injection. • No injection site reactions were noted in the preclinical studies. • In the GSK3511294 FTIH study 205722, injection site reactions were reported by one (3%) participant who received	• Daily monitoring of SAEs by Medical Monitor/SAE coordinator; regular systematic review of AE/SAE data from ongoing studies by GSK study team and/or GSK safety review team. • The IDMC will review unblinded safety data at regular intervals.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	GSK3511294 and one (8%) participant who received placebo.	
• QTc prolongation	• Four monkeys in the 6-month repeat dose monkey study administered 100 mg/kg every 3 months (2 doses) were observed to have QTc prolongation (mean change of 18 msec relative to vehicle control value) during Week 14. • In the GSK3511294 FTIH study (205722), a total of 2 participants had an elevated post-baseline QT interval corrected using Fridericia's formula (QTcF) value of potential clinical importance based on average from triplicate assessment: one on GSK3511294 100 mg SC (Week 2: 467 msec [all subsequent assessments were <450 msec and Day 1 pre-dose was 450 msec]) and one on placebo (Week 36: 455 msec [last assessment on study and Day 1 pre-dose was 414 msec]).	• ECGs will be performed according to timepoints specified in the SoA (Section 1.3) and the assessment will be done as specified in Section 8.3.3. • Participants with QTc prolongation on screening will be excluded (criterion 15, Section 5.2). • Participants with a pre-existing clinically significant cardiac medical condition are excluded (criterion 7, Section 5.2). • Participants who meet QT stopping criteria as specified in Section 7.1.2 will not receive another dose of study intervention. • The IDMC will review unblinded safety data at regular intervals.
• Risk of GSK3511294 affecting an unborn baby.	• Reproductive studies have not been conducted with GSK3511294; however, in the 6-month repeat dose monkey study no changes were observed in reproductive organs. Seminiferous tubules were evaluated with respect to their stage in the spermatogenic cycle and the integrity of the various cell types present within the different stages in sexually mature males.	• Participants who are pregnant, breastfeeding, or plan to become pregnant at Screening are excluded (criterion 19, Section 5.2). Participants who become pregnant during the study will not receive another dose of study intervention (see Section 7.1). • All female participants will be assessed at screening to determine childbearing status. Female participants of childbearing

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	No cell or stage specific abnormalities were noted. • In addition, there is a low reproductive risk associated with the IL-5 target mechanism (as shown in pre-clinical reproductive toxicology studies of mepolizumab and reslizumab), a low genotoxic concern for mAbs in general, and a low transfer of mAbs into semen due to the inability of large molecular weight proteins such as GSK3511294 to access pivotal cells in the testes [Setchell, 1975; Pollanen, 1995; Pollanen, 1989; Setchell, 2001; Sohn, 2016], the risk of adverse effects on spermatogenesis is considered minimal. Therefore, male participants are not required to use contraception.	potential must be using a highly effective contraceptive method from at least 14 days prior to first dose and until 30 weeks after the last administered dose as described in Section 10.4.2.
Study Procedures		
• Potential risk for injury with phlebotomy.	• Risks with phlebotomy include bruising, bleeding, infection, nerve damage.	• Procedures to be performed by trained personnel (i.e., study nurse).

2.3.2. Benefit Assessment

Current clinical data from approved anti-IL-5/5R mAbs (mepolizumab, reslizumab, and benralizumab) demonstrate clinical utility in the treatment of conditions associated with elevated eosinophil levels, such as severe asthma with an eosinophilic phenotype. Mepolizumab 100 mg SC (every 4 weeks) is approved as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype. The safety profile of mepolizumab is favourable.

As a LA anti-IL-5 mAb, GSK3511294 is anticipated to provide the same clinical benefit with a similar safety profile compared with mepolizumab and others in its class and with the added benefit of an extended duration of action requiring less frequent SC dosing (once every 6 months). As such, GSK3511294 may offer the convenience of an improved dosing schedule.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures being implemented to minimise risk to participants in this study, the potential risks of participating in this study are justified by the anticipated benefits that may be afforded to participants with severe uncontrolled asthma with an eosinophilic phenotype; therefore, the Sponsor considers that the investigation of the efficacy, and safety of GSK3511294 is justified in this study with a positive benefit: risk ratio.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks
Other	
• To investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	• Time to first clinically significant exacerbation[a] • Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit • Change from baseline in SGRQ total score at discrete timepoints during the 52-week period • Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period • SGRQ total score responder status at Week 52 (responder defined as achieving ≥4-point reduction from baseline) • ACQ-5 score responder status at Week 52 (responder defined as achieving ≥0.5-point reduction from baseline) • Change from baseline in Patient-Reported Outcomes Measurement Information Systems (PROMIS) Fatigue items score at

Objectives	Endpoints
	discrete timepoints during the 52-week period • Change from baseline in Asthma Daily Symptom Diary (ADSD)/ Asthma Nightly Symptom Diary (ANSD) weekly mean score at specified timepoints during the 52-week period • Change from baseline in awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean • Change from baseline in morning peak expiratory flow (PEF) 2-week mean • Change from baseline in daily asthma symptom scores 2-week mean • Change from baseline in mean number of occasions of rescue medication use/day 2-week mean • Mean number of days with oral corticosteroids (OCS) usage over 52 weeks • Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period • Change from baseline in Sino-nasal Outcomes Test-22 (SNOT-22) score at discrete timepoints during the 52-week period
• To investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient- and clinician-rated response to therapy • patient global impression of asthma severity and its change from baseline	• Patient-rated response to therapy at discrete timepoints during the 52-week period • Clinician-rated response to therapy at discrete timepoints during the 52-week period • Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period • Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during the 52-week period
• To investigate the PD effects of GSK3511294	• Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period

Objectives	Endpoints
• To investigate the PK of GSK3511294	• GSK3511294 plasma concentration at discrete timepoints during the 52-week period
Safety	
• To evaluate the safety and tolerability of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Incidence of AEs/SAEs • Laboratory parameters, including haematological and clinical chemistry parameters • Vital signs including blood pressure (BP), body temperature, and pulse rate • ECG assessments • Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294
Health Resource Use	
• To further evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on healthcare utilisation on top of existing asthma therapy	• Healthcare utilisation for asthma including hospitalisation, ED, and physician office/clinic visits

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

3.1. Primary Estimand

Population: Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Treatment comparison: GSK3511294 + SoC compared with placebo + SoC

Endpoint: Annualised rate of clinically significant exacerbations over 52 weeks

Main intercurrent events anticipated:

- Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e. regardless of the intercurrent event occurring
- Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be handled with a hypothetical strategy i.e. had the intercurrent event not occurred

- Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): to be handled with a treatment policy i.e. regardless of the intercurrent event occurring

Summary measure: Ratio of the rates of clinically significant exacerbations between GSK3511294 + SoC and placebo + SoC

For further details, see Section 9.4.

3.2. Secondary Estimands

Population: Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Treatment comparison: GSK3511294 + SoC compared with placebo + SoC

Endpoints:

- Change from baseline in SGRQ at Week 52
- Change from baseline in ACQ-5 at Week 52
- Change from baseline in pre-bronchodilator FEV_1 at Week 52
- Annualised rate of clinically significant exacerbations requiring hospitalisation and/or ED visit over 52 weeks

Main intercurrent events anticipated:

- Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e. regardless of the intercurrent event occurring
- Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be handled with a hypothetical strategy i.e. had the intercurrent event not occurred
- Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): to be handled with a treatment policy i.e. regardless of the intercurrent event occurring

Summary measures:

- Difference in mean change from baseline in SGRQ at Week 52
- Difference in mean change from baseline in ACQ-5 at Week 52
- Difference in mean change from baseline in pre-bronchodilator FEV_1 at Week 52
- Ratio of the rates of clinically significant exacerbations requiring hospitalisation and/or ED visit

between GSK3511294 + SoC and placebo + SoC.

For further details, see Section 9.4.

4. STUDY DESIGN

4.1. Overall Design

This study employs a multi-centre, randomised, placebo-controlled, double-blind, parallel group design. The study will recruit adults and adolescents (≥12 years) with a confirmed diagnosis of severe asthma with an eosinophilic phenotype and who are on a regimen of medium to high dose ICS (≥440 mcg fluticasone propionate [FP] hydrofluoroalkane product [HFA] daily, or clinically comparable [GINA, 2020; see Appendix 10]) plus at least one additional controller medication, with evidence of bronchodilator reversibility or airway hyperresponsiveness as measured by methacholine/histamine challenge. Eligible participants must have uncontrolled asthma with a history of repeat exacerbations (≥2 exacerbations in the previous 12 months) while on their existing maintenance asthma therapy that excludes any biologics. Participants will be required to have a blood eosinophil count of ≥150 cells/µL at screening or ≥300 cells/µL documented in the 12 months prior to screening. Participants who have received any anti-IL-5/5R mAb therapy within the last 12 months will be excluded from this study.

Participants will attend a Pre-screen Visit (Visit 0) to sign consent and a Screening Visit (Visit 1; may be done on the same day as Visit 0) for eligibility assessments (see Section 8.1). At the conclusion of the run-in period (Visit 2), participants who meet the pre-defined criteria (see Section 5.1 and Section 5.3) will be randomised in a 2:1 ratio to receive either GSK3511294 100 mg or placebo, administered SC (at Week 0 and Week 26) in the clinic via a pre-filled safety syringe (PFS) as an adjunct therapy. Randomisation will be stratified based on baseline ICS dose (medium [approximately 25% of participants] or high [approximately 75% of participants]; see Appendix 10). Participants will remain on their existing stable maintenance asthma therapy throughout the study (See Section 6.9 for details on concomitant medications). See Section 4.1.1 for additional details on the study phases, duration, and treatment arms.

The primary outcome measure will be the annualised rate of clinically significant exacerbations (i.e. exacerbations requiring systemic CSs and/or hospitalisation and/or ED visit [see Section 8.2.2]) measured over the 52-week treatment period. Additional efficacy assessments will include lung function (pre- and post-bronchodilator FEV_1), asthma control (ACQ-5), HRQoL measured with SGRQ, fatigue (PROMIS items), nasal symptoms (SNOT-22 questionnaire), daytime and night-time asthma symptoms (ADSD/ANSD), and daily electronic diary (eDiary) parameters including peak flow, rescue use, daily symptoms and nocturnal awakening due to asthma (see Section 8.2).

The study will include safety (see Section 8.3 and Section 8.4) and immunogenicity (see Section 8.8) assessments to characterise the safety profile of GSK3511294 100 mg SC following repeat dosing. In addition, blood samples will be collected for assessment of PD effects (blood eosinophils) (see Section 8.7) and PK of GSK3511294 (see Section 8.5).

After randomisation, all participants will be encouraged to remain in the study and complete all scheduled visits, regardless of whether they receive the second dose of study intervention at Week 26. Participants who experience any of the study intervention

discontinuation conditions (listed in Section 7.1) will not receive another dose of study intervention.

Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 10, Exit Visit 17, and WS Visit (if applicable). Participants who are unable to attend their scheduled clinic visits due to COVID-19 restrictions or other unexpected events may complete some visits at home (see Appendix 11). Note: study intervention will only be administered in the clinic (at Week 0 and Week 26 visits).

4.1.1. Study Phases, Duration and Treatment Arms

At pre-screening, participants will be requested to participate in the study for a maximum of 60 weeks (Visit 0 to the Exit Visit, inclusive) or 64 weeks if not continuing into the OLE Study 212895 (Visit 0 to the Follow-up Visit, inclusive).

During the study, participants will remain on their existing maintenance asthma therapy whilst completing all phases of the study described in Table 1.

Table 1 Study Phases

Phase	Phase Title	Duration	Description
1	Pre-screening (Visit 0)	0-2 weeks	Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) but must be completed prior to initiating any Visit 1 procedures
2	Screening (Visit 1) and Run-in	1-6 weeks	Participants who meet all the eligibility criteria at Screening (Visit 1) will enter the run-in period for a minimum of 1 week and a maximum of 6 weeks. The run-in is intended to assess the participant's compliance with study-related procedures and continued eligibility for the study as well as to collect baseline eDiary data. Participants who experience an asthma exacerbation during the run-in period should receive treatment for their exacerbation and remain in the run-in period until the investigator considers that the participant has returned to their baseline asthma status for at least one week. The participants that are not eligible to continue in the study at the end of the run-in period will be deemed run-in failures, but may be rescreened after consultation with the Medical Monitor (Section 5.5).

Phase	Phase Title	Duration	Description
3	Study Intervention (Visit 2-Visit 17)	52 weeks	Participants who meet the randomisation criteria will enter the 52-week treatment period and will be randomised to receive either add-on **GSK3511294 (100 mg) or matching placebo in a 2:1 ratio.** During the treatment phase, a total of 2 doses of study medication will be administered SC via PFS: at Week 0 (Visit 2) and Week 26 (Visit 10).[a] Clinic visits will occur at Week 0, Week 2, Week 4 and every 4 weeks thereafter with an additional clinic visit at Week 26 for the administration of the second dose of study intervention. The study intervention period will conclude with the Exit Visit at Week 52 (Visit 17).
Only participants who choose not to enter the OLE study will complete the phase below:			
4	Follow-up	4 weeks	Participants will complete a Follow-up visit/call 4 weeks after the Exit Visit; this visit/call will capture AE/SAE assessments and a urine pregnancy test result. At the end of the Follow-up visit/call, participants will be prescribed appropriate alternative asthma therapy at the physician's discretion, if required.

a. Participants who experience any of the study intervention discontinuation conditions listed in Section 7.1 will not receive another dose of study intervention but will be encouraged to remain in the study and complete their remaining scheduled visits/assessments.

4.1.2. Treatment after the End of Study

Participants who receive both doses of double-blind treatment and complete the Week 52 Exit Visit will be eligible to participate in the OLE study 212895. See Section 6.7 for details.

Participants who are not entering the OLE study 212895 will enter a 4-week follow-up period and complete the study with a Follow-up visit/call at Week 56. After study completion, appropriate alternative asthma therapy may be prescribed at the physician's discretion.

4.1.3. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilised in this study to ensure external objective review of the data in order to protect the ethical and safety interests of participants and to protect the scientific validity of the study (see Section 10.1.5).

4.2. Scientific Rationale for Study Design

Population: This study is designed to evaluate the efficacy and safety of GSK3511294 100 mg SC as an adjunct therapy in participants with severe uncontrolled asthma with an eosinophilic phenotype. Participants should have uncontrolled asthma, as evidenced by repeat exacerbations, despite treatment with optimised background therapy consisting of maintenance ICS treatment and at least one additional controller. Participants are also required to have the requisite elevated blood eosinophil count (see randomisation criterion 1, Section 5.3) that is indicative of asthma with an eosinophilic phenotype. This population has been shown to benefit from add-on anti-IL-5 therapies such as mepolizumab [Pavord, 2012, Ortega, 2014; Chupp, 2017] and is therefore anticipated to benefit from GSK3511294.

Blood eosinophil count screening: A Screening blood eosinophil count threshold of ≥150 cells/µL at Screening Visit 1 or ≥300 cells/µL in the previous 12 months has been selected as a criterion to identify participants likely to respond to treatment with anti-IL-5 therapy, consistent with findings from previous trials with mepolizumab.

Primary efficacy endpoint: A primary efficacy endpoint of annualised rate of clinically significant exacerbations has been selected as a robust and clinically relevant measure of the direct benefit of GSK3511294 to a population with severe uncontrolled asthma with an eosinophilic phenotype. In the current study, the definition of clinically significant exacerbations (see Section 8.2.2), i.e. exacerbations treated with systemic CSs (intramuscular [IM], intravenous [IV], or oral) for 3 or more days and/or hospitalisation and/or ED visit, is consistent with previous trials with mepolizumab [Pavord, 2012; Ortega, 2014] and reslizumab [Castro, 2015].

Placebo-control design: An established randomised, double-blind and parallel-group study design will allow for a robust determination of participant response to GSK3511294 as an adjunct therapy to their maintenance asthma therapy. As such, the comparator arm in this study will be placebo plus continued maintenance asthma treatment. A 2:1 randomisation will be used in order to limit the number of participants randomised to placebo treatment and to provide more safety information on GSK3511294. All participants will continue to receive their optimised and stable maintenance asthma therapy throughout the entire duration of the study regardless of intervention arm assignment. The stable maintenance asthma therapy (per the inclusion criteria) will consist of medium to high dose ICS (≥440 mcg FP HFA daily, or clinically comparable [GINA, 2020; see Appendix 10]) with at least one additional controller medication e.g., long-acting beta-2-agonist (LABA), with or without maintenance oral corticosteroids (OCS). Participants who are treated with medium dose ICS will also need to be treated with LABA to qualify for inclusion.

Study Duration: A 52-week treatment period should allow sufficient time to assess whether GSK3511294 100 mg SC, administered as two repeat doses 26 weeks apart (at Week 0 [randomisation] and at Week 26), can reduce the annualised rate of clinically significant exacerbations to a similar extent to that observed with other anti-IL-5 mAbs. The study will also provide 12-month safety data with repeat dosing.

Run-in Period: The one-week (maximum 6 weeks) Run-in period allows for the assessment of participant understanding and compliance with the daily eDiary, to establish Baseline symptoms, and to allow adequate time for receipt of results from assessments collected at Screening Visit 1.

Open-label extension study: Following study completion, all eligible participants will have the option to participate in the OLE study to provide additional safety data (see Section 6.7).

Data collection after discontinuation from study intervention: The protocol objective is to collect data over the full study period, whether participants continue on study intervention or in the case of premature discontinuation from study intervention. However, the decision to continue in the study after premature discontinuation from study intervention remains the prerogative of the participant. Participants who agree to continue in the study after premature discontinuation from study intervention (for any reason) will continue to be contacted by the study site, either through in clinic visits or by phone as agreed with the participant, on a monthly basis (aligned to their study schedule) until the end of their planned 52-week participation and follow up contact 4 weeks later, to enable capture of post-intervention information.

4.2.1. Participant Input into Design

Participant involvement in the study design was obtained from 10 patients (6 in Italy, 1 in UK, and 3 in US [1 adolescent]) using 2 online qualitative surveys containing 17 questions over a period of 2 weeks. Based on the participant feedback, the following design elements will be implemented:

- Reduced number of laboratory samples and patient-reported outcomes (PRO) assessments
- A hybrid trial model, allowing for home visits and virtual/telemedicine visits at key assessments which will reduce the burden of onsite visits and offer some flexibility in visit timing for the participant's schedule

4.3. Justification for Dose

The dose rationale for this study is supported by the FTIH Study 205722 [GlaxoSmithKline Document Number 2019N411063_00] that investigated single SC doses of GSK3511294 ranging from 2 mg to 300 mg. The FTIH study was designed to collect robust blood eosinophil pharmacology data (including washout) in a relevant population (mild to moderate asthma and a blood eosinophil count ≥200 cells/µL at screening) and inform dose selection in late-phase development using Model-informed drug development (MIDD) principles [Wang, 2019; Marshall, 2019]. The precedence of using blood eosinophil reduction as a predictor of efficacy in severe asthma with an eosinophilic phenotype was established in two mepolizumab Phase 3 studies, which consistently reduced annualised exacerbation rate by approximately 50%, for associated reductions in blood eosinophils of 84% in the MENSA trial [Ortega, 2014] and 78% in the MUSCA trial [Chupp, 2017], compared with placebo. Since GSK3511294 targets the same IL-5 epitope as mepolizumab, establishing the same reduction in blood eosinophils

as mepolizumab via the same IL-5 neutralisation is expected to generate the same clinical efficacy in the same patient population (i.e., severe asthma with an eosinophilic phenotype with a previous history of two or more exacerbations in the past 12 months). In addition, given the precedented safety profile of IL-5 neutralisation comparable to placebo, targeting previous mepolizumab pharmacology is both valid and expeditious in selecting the dose of GSK3511294.

A comprehensive analysis of the clinical effects of GSK3511294 on blood eosinophils from Study 205722 was therefore conducted to identify the dose and frequency of dosing that match previous Phase 3 mepolizumab target pharmacology most closely. To this end, a Bayesian non-linear mixed-effects dose-time response model was used to analyse blood eosinophil data. This model was then used to calculate the posterior probability of achieving reductions of 78% for the MUSCA trial [Chupp, 2017] and 84% for the MENSA trial [Ortega, 2014] compared with placebo. Doses deemed suitable were defined as having a probability of exceeding MUSCA in excess of 80% while doses deemed unsuitable as having a probability of exceeding MENSA of less than 10%.

Based on the comprehensive analysis of the clinical effects of GSK3511294 on blood eosinophils, a dose of 100 mg SC GSK3511294 administered every 26 weeks has been selected to match the pharmacology seen with mepolizumab in two Phase 3 studies at the approved therapeutic dose, but over an extended period of 26 weeks [GSK Document Number 2019N418119_00].

4.4. End of Study and Study Completer Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed the visit at Week 52, regardless of whether the second dose of study intervention (at Week 26) was received.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if **all** of the following criteria apply:

AGE
1. **Age:** Adults and adolescents ≥12 years of age, at the time of signing the informed consent/assent. [For countries where local regulations or the regulatory status of study medication permit enrolment of adults only, participants recruited will be ≥18 years of age]
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. **Asthma:** Participants must have a documented physician diagnosis of asthma for ≥2 years that meets the National Heart, Lung, and Blood Institute guidelines [NHLBI, 2007] or GINA guidelines [GINA, 2020] **AND** a) **Eosinophilic phenotype:** Have, or with high likelihood of having, asthma with an eosinophilic phenotype as per Randomisation Criteria 1 and 2 (see Section 5.3) **AND** b) **Exacerbation history:** Have previously confirmed history of ≥2 exacerbations requiring treatment with systemic CS (IM, IV, or oral), in the 12 months prior to Visit 1, despite the use of medium to high-dose ICS (see criterion 4). For participants receiving maintenance CS, the CS treatment for the exacerbations must have been a two-fold dose increase or greater. 3. **Airflow obstruction:** Persistent airflow obstruction as indicated by: a) For participants ≥18 years of age at Visit 1, a pre-bronchodilator FEV_1 <80% predicted (NHANES III) recorded at Visit 1 b) For participants 12-17 years of age at Visit 1: • A pre-bronchodilator FEV_1 <90% predicted (NHANES III) recorded at Visit 1 **OR** • FEV_1:Forced Vital Capacity (FVC) ratio <0.8 recorded at Visit 1
ASTHMA MAINTENANCE THERAPY
4. **Inhaled Corticosteroid:** A well-documented requirement for regular treatment with medium to high dose ICS (in the 12 months prior to Visit 1 with or without maintenance OCS). The maintenance ICS dose must be ≥440 mcg FP HFA daily, or clinically comparable [GINA, 2020; see Appendix 10]. Participants who are

treated with medium dose ICS will also need to be treated with LABA to qualify for inclusion.

5. **Additional Controller Medication:** Current treatment with at least one additional controller medication, besides ICS, for at least 3 months [e.g., LABA, long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonist (LTRA), or theophylline].

SEX

6. **Male or eligible female.**

   Female Participants:

   - A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
     - Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4.1

       OR

     - Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4.2 from at least 14 days prior to the first dose of study intervention until at least 30 weeks after the last administered dose of study intervention.
   - A WOCBP must have a negative highly sensitive serum pregnancy test at screening Visit 1 and a negative highly sensitive urine pregnancy test within 24 hours before the first dose of study intervention. Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.
   - Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
   - The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated in relationship to the first dose of study intervention).
   - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

INFORMED CONSENT

7. **Informed Consent:** Capable of giving signed informed consent/assent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

French participants: In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

MEDICAL CONDITIONS

1. **Concurrent Respiratory Disease:** Presence of a known pre-existing, clinically important lung condition other than asthma. This includes (but is not limited to) current infection, bronchiectasis, pulmonary fibrosis, bronchopulmonary aspergillosis, or diagnoses of emphysema or chronic bronchitis (chronic obstructive pulmonary disease other than asthma) or a history of lung cancer.
2. **Eosinophilic Diseases:** Participants with other conditions that could lead to elevated eosinophils such as hyper-eosinophilic syndromes including (but not limited to) Eosinophilic Granulomatosis with Polyangiitis (EGPA, formerly known as Churg-Strauss Syndrome) or Eosinophilic Esophagitis.
3. **Parasitic infection:** Participants with a known, pre-existing parasitic infestation within 6 months prior to Visit 1.
4. **Immunodeficiency:** A known immunodeficiency (e.g. human immunodeficiency virus – HIV), other than that explained by the use of CSs taken as therapy for asthma.
5. **Malignancy:** A current malignancy or previous history of cancer in remission for less than 12 months prior to screening (Participants that had localised carcinoma of the skin which was resected for cure will not be excluded).
6. **Liver Disease:** Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice.

   NOTE: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) are acceptable if participant otherwise meets entry criteria.
7. **Other Concurrent Medical Conditions:** Participants who have known, pre-existing, clinically significant cardiac, endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.
8. **Vasculitis:** Participants with current diagnosis of vasculitis. Participants with high clinical suspicion of vasculitis at screening will be evaluated and current vasculitis must be excluded prior to enrolment.
9. **COVID-19:** Participants that, according to the investigator's medical judgment, are likely to have active COVID-19 infection should be excluded. Participants with known COVID-19 positive contacts within the past 14 days should be

excluded for at least 14 days following the exposure during which the participant should remain symptom-free.

PRIOR/CONCOMITANT THERAPY

10. **Monoclonal antibodies targeting IL-5/5R:** Participants who have received mepolizumab (Nucala), reslizumab (Cinqair/Cinqaero), or benralizumab (Fasenra) within 12 months prior to Visit 1 or who have a previous documented failure with anti-IL-5/5R therapy.
11. **Other mAbs in the treatment of asthma**: Participants who have received omalizumab (Xolair) or dupilumab (Dupixent) within 130 days prior to Visit 1.
12. **Other mAbs not used for the treatment of asthma:** Participants who have received any mAb within 5 half-lives of Visit 1.
13. **Investigational Medications:** Participants who have received treatment with an investigational drug within the past 30 days or five terminal phase half-lives of the drug whichever is longer, prior to Visit 1 (this also includes investigational formulations of marketed products).

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

14. **Previous participation:** Previously participated in any study with mepolizumab, reslizumab, or benralizumab and received study intervention (including placebo) within 12 months prior to Visit 1.

DIAGNOSTIC ASSESSMENTS

15. **ECG Assessment:** QTcF ≥450 msec or QTcF ≥480 msec for participants with Bundle Branch Block at screening Visit 1.

OTHER EXCLUSIONS

16. **Smoking history:** Current smokers or former smokers with a smoking history of ≥10 pack years (number of pack years = (number of cigarettes per day / 20) x number of years smoked). A former smoker is defined as a participant who quit smoking at least 6 months prior to Visit 1.
17. **Alcohol/Substance Abuse:** A history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1.
18. **Hypersensitivity:** Participants with allergy/intolerance to a mAb or biologic.
19. **Pregnancy:** Participants who are pregnant or breastfeeding. Participants should not be enrolled if they plan to become pregnant during the time of study participation. Requirements for pregnancy testing are located in Section 8.3.5.

20. **Adherence:** Participants who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations.

5.3. Randomisation Criteria

At the end of the run-in period, study participants must fulfil all of the randomisation inclusion/exclusion criteria below in order to be randomised to study intervention.

5.3.1. Randomisation Inclusion Criteria

RANDOMISATION INCLUSION CRITERIA

1. **Blood eosinophil count:**
   a) An elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past 12 months prior to Visit 1 that is related to asthma

      OR

   b) An elevated peripheral blood eosinophil count of ≥150 cells/μL at Screening Visit 1 that is related to asthma.
2. **Asthma:** Evidence of airway reversibility or responsiveness as documented by either:
   a) Airway reversibility (FEV_1≥12% and 200 ml) demonstrated at Visit 1 or Visit 2 using the Maximum Post Bronchodilator Procedure **OR**
   b) Airway reversibility (FEV_1≥12% and 200ml) documented in the 12 months prior to Visit 2 (randomisation visit) **OR**
   c) Airway hyperresponsiveness (methacholine: PC_{20} of <8 mg/mL, histamine: PD_{20} of <7.8 μmol, mannitol: decrease in FEV_1 as per the labelled product instructions) documented in the 12 months prior to Visit 2 (randomisation visit)
3. **eDiary compliance:** Compliance with completion of the eDiary defined as completion of all questions on 4 or more days out of the 7 days immediately preceding Visit 2.

5.3.2. Randomisation Exclusion Criteria

RANDOMISATION EXCLUSION CRITERIA

1. **Laboratory abnormality:** Evidence of clinically significant abnormality in the haematological, biochemical or urinalysis screen at Visit 1, as judged by the investigator.
2. **Liver chemistry test:** Participants who meet the following based on results from sample taken at Screening Visit 1:
   a) Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)

b) Total bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

c) Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice.

NOTES: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) is acceptable if the participant otherwise meets entry criteria.

3. **ECG:** Evidence of a clinically significant abnormality in the 12-lead ECG over-read conducted at Screening Visit 1, based on the evaluation of the investigator, **OR** QTcF ≥450msec or QTcF ≥480 msec for participants with Bundle Branch Block, at randomisation Visit 2.
4. **Unstable Asthma:** Participants with a clinically significant asthma exacerbation in the 7 days prior to randomisation should have their randomisation visit delayed until the investigator considers the participant's asthma to be stable (see Section 5.6).
5. **Maintenance Asthma Therapy:** Any changes in the dose or regimen of baseline ICS and/or additional controller medication (except for treatment of an exacerbation) during the run-in period.

5.4. Lifestyle Considerations

No lifestyle restrictions are required for this study.

5.5. Pre-screen/Screen/Run-in Failures

Pre-screen/screen/run-in failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any SAEs.

For the purposes of this study, pre-screen/screen/run-in failures will be defined as follows:

Pre-screen Failures	Screen Failures	Run-in Failures
Participants who are assigned a study number at the time of signing the informed consent (pre-screen visit) but do not progress to the screening visit.	Participants who complete at least one additional Visit 1 (Screening) procedure but do not enter the run-in period.	Participants who enter the run-in period but are not subsequently randomised.

Re-screening of participants will be permitted; however, advance written approval to proceed with re-screening a participant must be obtained from the Medical Monitor.

Re-screened participants should be assigned a new participant number for every screening/rescreening event.

5.6. Criteria for Temporarily Delaying Randomisation

Participants who experience a clinically significant asthma exacerbation during the run-in period should receive treatment for their exacerbation, have their randomisation visit delayed and remain in the run-in period (up to 6 weeks) until the investigator considers the participant to have returned to their baseline asthma status for at least 7 days.

A clinically significant exacerbation is defined as worsening of asthma requiring the use of systemic CS and/or hospitalisation and/or ED visit (Section 8.2.2).

A participant who is not eligible to continue in the study at the end of the run-in period, should be considered a run-in failure but may be rescreened after consultation with the Medical Monitor (Section 5.5).

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s)/product(s) (IP), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Study intervention will only be administered in the clinic; hence Visit 2 (Week 0) and Visit 10 (Week 26) are required to be in-clinic visits.

6.1. Study Intervention Administered

GSK3511294 is a humanised IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. GSK3511294 liquid drug product will be supplied by GSK in a Type I glass syringe (with a 1/2-inch, 29-gauge thin wall, staked needle and sealed with a latex-free rubber plunger). The drug product and syringe will be assembled in a single use, disposable safety syringe to enable delivery of the drug product. Each device enables SC delivery of 100 mg GSK3511294 in 1.0 mL sterile liquid formulation. The formulation contains L-histidine, trehalose dihydrate, L-arginine hydrochloride, disodium edetate (EDTA), water for injection and polysorbate 80.

The placebo in this study will be 0.9% sodium chloride solution contained in a PFS also supplied by GSK.

An overview of study intervention is provided in Table 2.

Table 2 Overview of Study Intervention

ARM Name	GSK3511294 100 mg	Placebo
Intervention Name	GSK3511294 100 mg SC	Placebo
Type	Biologic	N/A
Dose Formulation	Sterile liquid formulation in single-use PFS	Sterile 0.9% (w/v) sodium chloride solution in single-use PFS
Unit Dose Strength(s)	100 mg/mL; 1.0 mL (deliverable)	N/A, 1.0 mL (deliverable)
Dosage Level(s)	100 mg once every 26 weeks (Week 0 and Week 26)	Placebo once every 26 weeks (Week 0 and Week 26)
Route of Administration	SC injection	SC injection
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	Study Intervention will be provided in PFS. Each PFS will	Study Intervention will be provided in PFS. Each PFS will

	be labelled as required per country requirement.	be labelled as required per country requirement.

PFS=Pre-filled safety syringe, IMP=Investigational Medicinal Product, N/A=not applicable

6.1.1. Medical Devices

The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are injection devices:

- A pre-filled syringe contained within a safety syringe. The devices used in the study are representative of the devices planned to be marketed for the product.
- The components that comprise the pre-filled syringe (glass barrel with pre-staked needle and plunger) are sourced from Becton Dickinson. The pre-filled syringe is filled with study intervention (GSK3511294 or placebo) and assembled at GSK, Barnard Castle.
- The safety syringe components are manufactured by Becton Dickinson. The safety syringe components are assembled with the pre-filled syringe at GSK, Barnard Castle.

The Instruction for use (IFU) of the injection device will be provided. The instructions were developed and optimised as a result of formative human factors studies for mepolizumab and are representative of those that are planned for GSK3511294.

All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the investigator throughout the clinical investigation (see Section 8.4.8) and appropriately managed by GSK.

6.2. Packaging and Labelling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.3. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention.
- All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Further guidance and information for the final disposition of unused study intervention are provided in the SRM.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.4. Measures to Minimise Bias: Randomisation and Blinding

6.4.1. Treatment Assignment

- Eligible participants will be centrally randomised using an IRT system.
- The randomisation schedule will be generated using the GSK validated randomisation software RandAll NG. Separate randomisation schedules will be created for each country. Participants will be assigned to study intervention in accordance with the randomisation schedule. Once a randomisation number has been assigned to a participant, it cannot be reassigned to any other participant in the study.
- Randomisation will be stratified according to the participant's baseline ICS dose (medium [approximately 25% of participants] or high [approximately 75% of participants]; see Appendix 10).
- At Visit 2 (Week 0), those participants who meet the randomisation criteria will be randomised in a 2:1 ratio to receive one of the following study treatments in addition to their stable maintenance asthma treatment:
    - GSK3511294 100 mg SC
    - Placebo SC
- Study intervention will be administered in the clinic at Visit 2 (Week 0) and Visit 10 (Week 26) as per the SoA (Section 1.3).

6.4.2. Blinding

- The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours after breaking the

blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.

- Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, GSK3511294 and placebo will be administered from PFSs that will be identical in appearance.
- If a participant's intervention code is unblinded by the investigator or treating physician, that participant will continue with all study visits but will not receive the second dose of study intervention at Week 26. The primary reason for the event or condition which led to the unblinding will be recorded in the CRF (see Section 7.1).
- To maintain the blind, haematology data (absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes) from post-randomisation samples will not be reported to the site or the central study team.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.5. Study Intervention Compliance

Both doses of GSK3511294 or placebo will be administered under medical supervision via SC injection to participants by the investigator or designee at the study site. Dose administration details (date and time) will be recorded in the source documents and reported in the CRF.

Participants will be monitored in clinic for a minimum of 2 hours post-dose to monitor for immediate hypersensitivity and any other untoward effects. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of GSK3511294, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care if appropriate.

6.6. Dose Modification

Dose modification is not allowed.

6.7. Continued Access to Study Intervention after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition whether or not GSK is providing specific post-study treatment.

At the end of the study, participants will be eligible to screen to enter the OLE Study 212895 and have continued access to open-label GSK3511294 if he/she:

- has received both doses of study intervention (at Week 0 and Week 26), AND
- completed the scheduled Exit Visit at Week 52, AND
- did not meet any of the study intervention discontinuation conditions (Section 7.1) during the study.

For participants who enrol into the 12-month OLE study, the Day 1 visit of the OLE study can occur on the same day as the Exit Visit of the current study. Specific details on the OLE study will be documented separately.

Participants who do not enter the OLE study will complete a follow-up visit/call and be prescribed alternative asthma therapy if needed and as determined by the study investigator.

6.8. Treatment of Overdose

The dose of GSK3511294 that is considered to be an overdose has not been defined. There are no known antidotes and there is no specific treatment for a suspected overdose. In FTIH study 205722 (refer to the current IB [GlaxoSmithKline Document Number 2016N295843_03 or later]), single SC doses of GSK3511294 up to 300 mg were well tolerated by adult participants with mild/moderate asthma (6 participants received a 300 mg SC dose).

Each PFS will enable the delivery of a single dose of study intervention (see Section 6.1). In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Treat the participant with active supportive care as dictated by the participant's clinical status in the knowledge of the long half-life (approximately 41 days) of GSK3511294.
- Closely monitor the participant for AE/SAE and laboratory abnormalities for 30 weeks following the last administered dose.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding discontinuation or delay of another dose of study intervention will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.9. Concomitant Therapy

At pre-screening and/or screening, information on the participant's baseline maintenance asthma therapy will be collected and recorded in the eCRF.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded in the eCRF along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency (any dose changes are to be recorded for OCS)

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Permitted Medications and Non-Drug Therapies

Throughout the study, participants are to be maintained on their baseline maintenance asthma treatment consisting of ICS plus at least one other controller, e.g. LABA, LAMA, with or without maintenance OCS (see inclusion criteria 4 and 5, Section 5.1). It is recognised that in a year-long study, changes may need to be individualised if clinically crucial for a participant. The investigator is encouraged to discuss any cases with the Medical Monitor before initiating changes to a participant's maintenance asthma medication.

Additional asthma medications such as theophyllines and anti-leukotrienes will be permitted provided that they have been taken regularly in the 3 months prior to screening (Visit 1). If uncertain whether a medication is permitted, please confirm with the Medical Monitor.

Albuterol/salbutamol is permitted throughout the study but should be withheld in the 6-hour period prior to spirometry assessments, if possible. Study-provided albuterol/salbutamol should not be recorded in the eCRF, only in the eDiary.

LABAs, LAMAs, and fixed dose combinations of ICS/LABA or ICS/LABA/LAMA should be withheld for ≥12 hours prior to spirometry, if possible.

Continuous Positive Airway Pressure (CPAP) or Bilevel Positive Airway Pressure (BiPAP) for the treatment of obstructive sleep apnoea is permitted, if initiated prior to the Screening Visit (Visit 1). This treatment must be captured in the eCRF.

Allergen-specific immunotherapy is permitted provided that it has been taken regularly in the 6 months prior to screening (Visit 1).

6.9.2. Prohibited Medications and Non-Drug Therapies

The following medications are not allowed prior to screening (Visit 1), according to the following schedule, or during the study:

Medication	**Washout Time Prior to Screening Visit**
Investigational drugs	1 month or 5 half-lives whichever is longer
Omalizumab [Xolair], dupilumab [Dupixent]	130 days
Mepolizumab [Nucala], reslizumab [Cinqair/Cinqaero], benralizumab [Fasenra]	12 months
Other monoclonal antibodies	5 half-lives
Experimental anti-inflammatory drugs (non biologicals)	3 months

Immunosuppressive medications such as those listed below (not all inclusive)
Corticosteroids if used to treat a condition other than asthma • Intramuscular, long-acting depot • Regular systemic (oral or parenteral)
Methotrexate, troleandomycin, cyclosporin, azathioprine
Oral gold
Chemotherapy used for conditions other than asthma

Additionally, Bronchial Thermoplasty and Radiotherapy are excluded for 12 months prior to Visit 1 and throughout the study. CPAP, BiPAP, and oxygen therapy should not be initiated during the run-in period.

6.9.3. Rescue Medicine

Trade label albuterol/salbutamol metered dose inhalers (MDIs) will be provided as rescue medication throughout the study. Albuterol/salbutamol will be sourced locally for all centres.

Participants will be dispensed an MDI at Screening Visit 1 to be used primarily to treat asthma symptoms on an as needed basis and also during the reversibility assessments (see Section 8.2.3.1). The MDI should be replaced as needed.

Although the use of rescue medications is allowable (at any time during the study), the use of rescue medications should be withheld, if possible, for at least 6 hours prior to the spirometry assessments. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded in the eDiary.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

No further doses of study intervention will be administered to participants who meet any of the following permanent treatment discontinuation conditions at any time during the study treatment period:

- Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria (see Section 7.1.1)
- ECG: Meets any of the protocol-defined QTc stopping criteria (see Section 7.1.2)
- Pregnancy: Positive pregnancy test (see Section 8.4.5)
- Severe allergic reaction/anaphylaxis: Participants with severe allergic reaction/anaphylaxis with no clear alternative cause (see Appendix 8)
- Vasculitis: Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation (see Section 7.5).
- Study treatment unblinded: Unblinding of the study treatment assigned to a participant (see Section 6.4.2).

If a participant meets any of the treatment discontinuation conditions or chooses (for any reason) not to receive another dose of study intervention before the end of the protocol specified randomised intervention period:

- The investigator will make every effort to encourage the participant to remain in the study **and** to continue with all remaining study visits, including the Exit and Follow-up Visits.
- The primary reason for discontinuation of study intervention (e.g., AE, lack of efficacy, protocol deviation, investigator discretion, consent withdrawn etc.) must be recorded in the eCRF.
- Participants will be provided with the option to continue their scheduled visits in-clinic, at home, or by phone. The required study assessments will depend on whether the participant is attending the visit in-clinic, at home, or by phone. At a minimum, an assessment of exacerbations, AEs, SAEs, and concomitant medications will be completed.
- If for any reason, the participant later chooses to withdraw from the study, a Withdraw from Study Visit (see Section 7.2) should be conducted according to the SoA (Section 1.3).

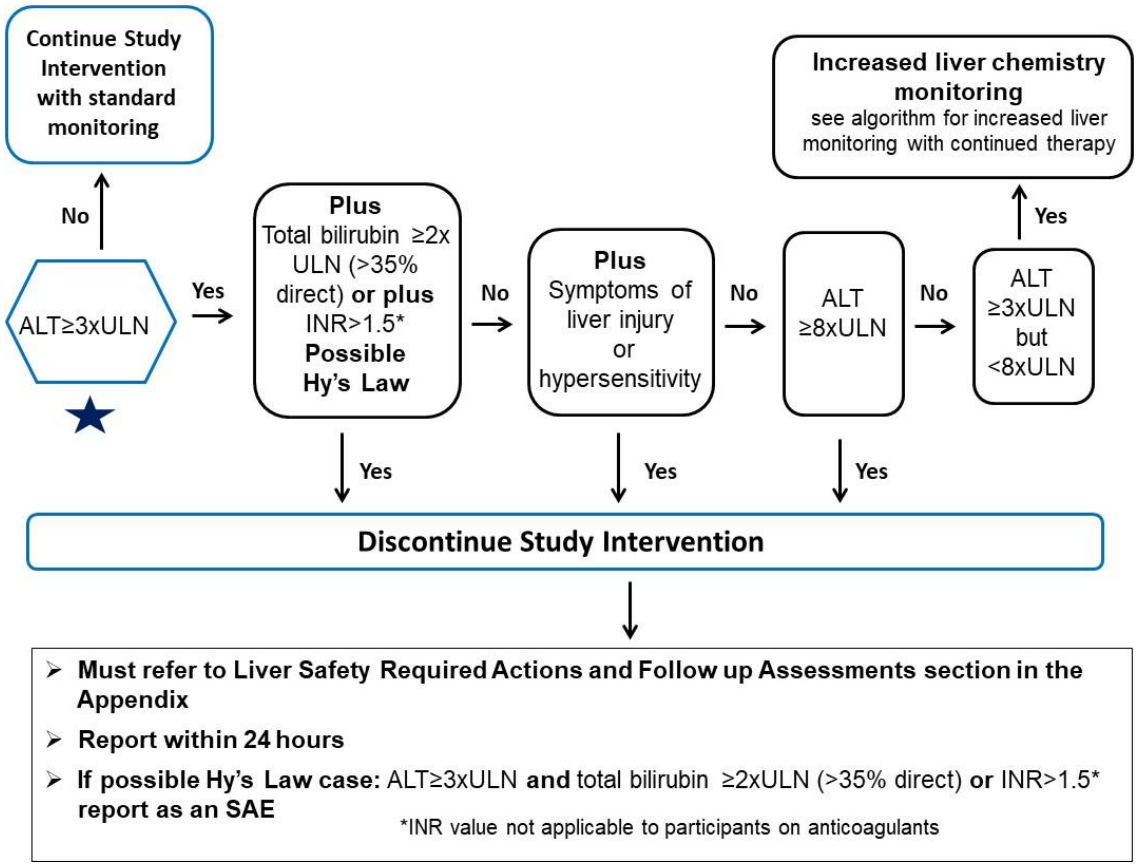
7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping criteria, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, the investigator believes that it is in the best interest of the participant.

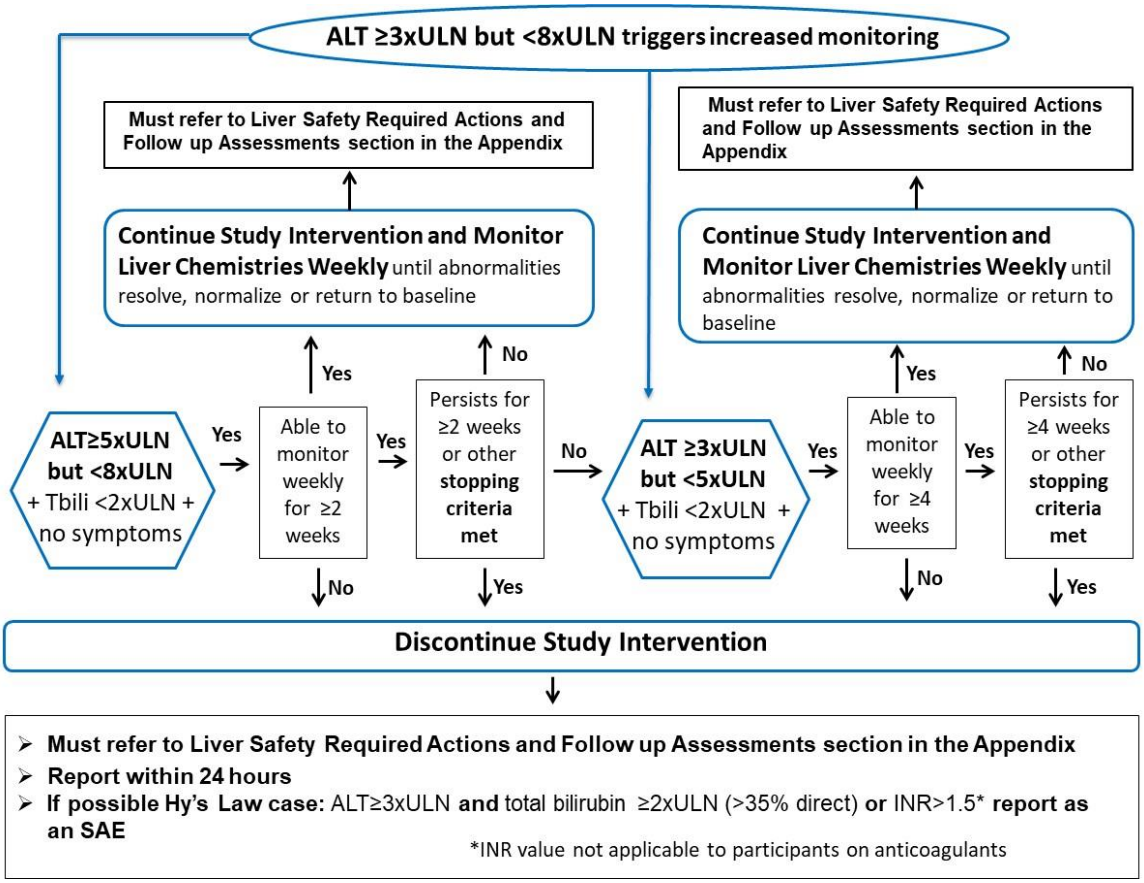
Liver Chemistry Stopping Criteria Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalised ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin

Refer to Appendix 6 for required Liver Safety Actions, Monitoring, and Follow-up Assessments.

Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT ≥3xULN but <8xULN and do not meet any of the liver stopping criteria



Abbreviations: ALT = alanine transaminase; Tbili = total bilirubin; INR = international normalised ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin.

Refer to Appendix 6 for required Liver Safety Actions, Monitoring and Follow-up Assessments.

7.1.1.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by a participant in this study will not be permitted.

7.1.2. QTc Stopping Criteria

Details on performing ECG assessments can be found in Section 8.3.3.

The QT interval corrected using Fridericia's formula (QTcF) must be used for *each individual participant* to determine eligibility for and discontinuation from the study intervention. This formula may not be changed or substituted once the participant has been enrolled.

For this study, the following QTc stopping criteria will apply:

- QTcF >500 msec OR uncorrected QT >600 msec
- Change from baseline of QTcF >60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTcF with Bundle Branch Block	**Discontinuation QTcF with Bundle Branch Block**
<450 msec	>500 msec
450 – 480 msec	≥530 msec

7.1.3. Temporary Discontinuation

For this study, a temporary discontinuation refers to a delayed administration of the second dose of study intervention at Week 26.

If a participant becomes infected (parasitic infection) during the study intervention period before receiving the second dose of study intervention and does not respond to anti-helminth treatment, a delayed administration of the study intervention may be considered in consultation with the GSK Medical Monitor.

7.2. Participant Discontinuation/Withdrawal from the Study

- Participants are strongly encouraged to remain in the study for the entire duration but may prematurely withdraw from the study at any time at his/her own request, at the request of their legally authorised representative (LAR), or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.
- Participants who prematurely withdraw from the study should attend:
  - a Withdraw from Study (WS) Visit, 26 weeks after the last administered dose of study intervention (at Week 26 or Week 52) **AND**
  - a Follow-up visit/call, 30 weeks after the last administered dose of study intervention for AE/SAE and pregnancy assessments.

  Note: this includes any participants who initially discontinue study intervention and remain in the study (Section 7.1) but later decide to withdraw from the study.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits (or scheduled phone calls, if applicable) and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study. A final attempt will be made to contact the participant for a safety follow-up 30 weeks after the last administered dose of study intervention.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

7.4. Reasons for Study Intervention Discontinuation and/or Study Withdrawal

The primary reason for study intervention discontinuation and/or study withdrawal will be recorded in the eCRF. When a participant withdraws consent, the investigator must document the reason (if specified by the participant) in the eCRF.

7.5. Criteria for Follow-up of Potential Type III Hypersensitivity (Immune Complex Disease /Vasculitis)

Owing to the adverse findings of arterial inflammation that were observed in the 1-month, but not 6-month, nonclinical toxicology studies, events potentially representing type III hypersensitivity/immune complex disease/vasculitis should be promptly reported to GSK, and consultation with the Medical Monitor is encouraged. Treatment for the event will be given as medically required. If possible, PK, ADA, C3, and C4 samples may be taken at the time of the event along with haematology, clinical chemistry and urinalysis.

Symptoms potentially suggestive of vasculitis include but are not limited to:

- persistent* fever (*where persistent is considered to be a duration of ≥2 days)
- persistent* muscle and joint pain

- persistent* rash
- persistent* fatigue
- symptoms of peripheral neuropathy, like numbness or weakness
- laboratory abnormalities, e.g., decreased platelets, elevated creatinine, decrease in complement C3/C4, abnormal urinary albumin/creatinine ratio

Participants who experience any of the above events should be monitored until the event resolves and/or a diagnosis is established.

The symptoms and clinical features are often non-specific and heterogenous with respect to the time course over which they develop, organ involvement and the constellation of symptoms and severity. Early recognition of potential events of vasculitis is important to timely diagnosis and subsequent treatment.

The precise management will depend on the clinical evaluation at the time of presentation and ongoing assessment including consideration of relevant differential diagnoses. Given that there is often a differential for presenting symptoms such as infection, and indeed such factors may also precipitate immune related AEs, these factors (infectious, neoplastic, metabolic, toxic) should be given due consideration and ruled out.

Serological, immunological, and histological (biopsy) data should be considered to support the diagnosis and consultation with the GSK Medical Monitor, and an appropriate medical specialist should be considered when investigating a possible immune related AE.

Unscheduled PK, ADA, C3 and C4 samples may be taken at the time of the event and samples may be taken for additional biomarkers (e.g., antinuclear antibodies [ANA], anti-neutrophil cytoplasmic antibodies [ANCA]) in the setting of clinical concern regarding the possibility of immune complex disease. If necessary, testing for biomarkers, e.g., ANA, ANCA (anti-myeloperoxidase [MPO] antibody and anti-proteinase 3 [PR3] antibody), may also be conducted using the frozen baseline serum samples (that were collected and stored prior to administration of study intervention) to allow for evaluation of interval change for participants with suspected vasculitis (see Section 8.7.2). Other possible causative or differential factors for abnormal clinical or laboratory observations may also have to be investigated including testing to exclude infection.

If clinically indicated, the participant may be referred to a specialist for further management, which may include organ biopsy.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Section 1.3).
- As detailed in the SoA (Section 1.3), participants who are not entering the OLE study 212895 should make every effort to complete the Week 56 follow-up visit/call on the scheduled day. The visit may be completed within 7 days of the scheduled time-point.
- Every effort should be made to reduce missing data throughout the study.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue to receive the second scheduled dose of study intervention, if applicable.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilised for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Laboratory results that could unblind the study (e.g., haematology differential [absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes]) will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Participants should be provided a quiet space in which to complete patient-reported outcomes (PRO), prior to other assessments and procedures. Site staff can provide limited advice if required, however participants should not be guided or directed in answering questions. Family or friends should not influence the answers. Site staff should encourage participants to complete all questions.

8.1. Screening and Critical Baseline Assessments

8.1.1. Pre-screening Visit (Visit 0)

Informed consent should be obtained at the Pre-screening Visit or the Screening Visit, prior to initiating any study assessments. A participant number will be assigned at the time the ICF is signed. Participants can conduct the Pre-screening Visit (Visit 0) up to 2 weeks prior to the Screening Visit (Visit 1).

The pre-screening procedures will include a review/assessment of:

- Inclusion/exclusion criteria (see Section 5.1 and Section 5.2)
- Demographic information including gender, ethnic origin, race, and year of birth (can be conducted at Visit 1 instead, if necessary)
- Childbearing status for all women (can be conducted at Visit 1 instead, if necessary); for WOCBP, contraception should be started at least 14 days prior to receiving the first dose of study intervention (see Appendix 4)
- Therapy history and concomitant medications including maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications

All clinic visits from Pre-screening Visit 0 to the Exit Visit (or if applicable, the WS Visit or the Follow-up Visit) must be registered in the IRT and the relevant eCRF form completed.

Serious adverse events must be collected from signing of Informed Consent if considered related to study procedures.

8.1.2. Critical Assessments performed at Screening (Visit 1)

The following critical assessments will be conducted at Screening Visit 1:

- Review inclusion/exclusion criteria (see Section 5.1 and Section 5.2)
- Review therapy history and concomitant medications including maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications.
- Medical history including:
  - Asthma including current treatment, duration of asthma, courses of rescue CSs, history of previous intubations, asthma exacerbation history in previous year, asthma triggers
  - Cardiovascular (CV) medical history/risk factors (as detailed in the eCRF)
  - Vasculitis, allergies and anaphylaxis history
  - Smoking history and current status
  - Historical blood eosinophil count - participants without a documented blood eosinophil count ≥300 cells/µL in the 12 months prior to Screening Visit 1 must show a blood eosinophil count ≥150 cells/µL, based on the sample collected at Visit 1 (see randomisation criterion 1, Section 5.3.1).
- Spirometry including bronchodilator responsiveness testing using the Maximum Bronchodilator Procedure (see Section 8.2.3)
- PGI-S (see Section 8.2.8)
- Safety Assessments including:
  - Physical exam (see Section 8.3.1)
  - Vital signs (see Section 8.3.2)

  - Resting 12-lead ECG (see Section 8.3.3)
  - AE/SAE assessment
- Blood/urine sample collection for the following laboratory tests (see Section 8.3.4):
  - Haematology with differential
  - Clinical chemistry (including liver chemistry)
  - Serum pregnancy test – for all WOCBP (childbearing potential for all women will be assessed at pre-Screening) (see Section 8.3.5)
  - Urinalysis (can be conducted at Visit 2 instead, if necessary)
  - Parasitic screening (only in regions with high-risk or for participants who have visited a high-risk region in the past 6 months)
- eDiary registration and training
- Provide medical problems and healthcare utilisation worksheet (see Section 8.9)
- Complete ADSD/ANSD (to be completed daily at home; see Section 8.2.10)

8.1.3. Critical Assessments performed at Randomisation (Visit 2)

The following critical assessments will be conducted at randomisation Visit 2:

Review of randomisation criteria (see Section 5.3), and data collected at Visit 1, including, if applicable, verification that the asthma-related peripheral blood eosinophil count is ≥150 cells/μL, based on the sample collected at Visit 1

- Review of concomitant medications
- Spirometry (if airway reversibility was not demonstrated at Visit 1, the Maximum Bronchodilator Procedure may be repeated at Visit 2) (see Section 8.2.3)
- SGRQ (see Section 8.2.4)
- ACQ-5 (see Section 8.2.5)
- SNOT-22 (see Section 8.2.7)
- Review eDiary asthma symptoms and PEF summary report
- PGI-S (see Section 8.2.8)
- Safety assessments including:
  - Vital signs (see Section 8.3.2)
  - Resting 12-lead ECG (see Section 8.3.3)
  - AE/SAE assessment
- Blood/urine sample collection for the following laboratory tests (see Section 8.3.4):
  - Haematology with differential

- Total IgE
- Clinical chemistry (including liver chemistry)
- Urine pregnancy test – for all WOCBP (see Section 8.3.5)
- Complement C3 and C4
- PK (see Section 8.5)
- Baseline immunogenicity (see Section 8.8)
- Storage of a baseline sample that may be analysed for the presence of ANCA (anti-MPO antibody and anti-PR3 antibody tests), ANA, and anti-dsDNA antibody, if necessary (see Section 7.5)
- Storage of a baseline sample (with the participant's consent and where permitted) that may be analysed for exploratory biomarkers (see Section 8.7.3)

- Provide and review medical problems and healthcare utilisation worksheet (see Section 8.9)

The following items will be completed at home:

- PROMIS Items (see Section 8.2.6)
- Complete ADSD/ANSD daily (see Section 8.2.10)

8.2. Efficacy Assessments

8.2.1. Efficacy Endpoints

Efficacy endpoints and estimands are provided in Section 3.

8.2.2. Asthma Exacerbations

Clinically significant exacerbations of asthma are defined by:

Worsening of asthma which requires use of systemic CSs[1] and/or hospitalisation and/or Emergency Department (ED) visit.

[1]*For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.*

Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

Additional details on the process for determination of clinically significant exacerbations can be found in the Statistical Analysis Plan (SAP).

Details of each asthma exacerbation, including medications used to treat exacerbations should be recorded in the eCRF.

Asthma exacerbations should not be recorded as an AE unless they meet the definition of a SAE.

The time period for collection of exacerbation information in the eCRF will be from the start of study intervention until the Exit Visit or Follow-up Visit if applicable.

8.2.3. Pulmonary Function Testing/ Spirometry

Spirometry lung function assessments will be performed for all participants at specified visits to assess FEV_1. At least 3 valid spirometry efforts should be attempted (with no more than 8 attempts) using the ATS guidelines [Miller, 2005]. Spirometry includes FEV_1, percent predicted FEV_1, Forced Vital Capacity (FVC) and FEV_1/FVC. Spirometry assessments will be performed at screening (Visit 1), randomisation (Visit 2), and at scheduled in-clinic visits according to the SoA (Section 1.3). At each visit, spirometry should be performed at the same time of day (±1 hour) as the assessment performed at Visit 2 (the baseline assessment). Participants should try to withhold short-acting beta-2-agonists (SABAs) for ≥6 hours and LAMAs/LABAs for ≥12 hours prior to the clinic visit, if possible.

Spirometry should not be conducted for participants with confirmed/suspected COVID-19.

8.2.3.1. Reversibility using the Maximum Post-Bronchodilator Method

Pre-bronchodilator measurements will be taken at the clinic visits specified in the SoA (Section 1.3): at screening, randomisation, Week 26 Visit, and Exit Visit (or EW Visit). In addition, post-bronchodilator values will be recorded following reversibility testing using the Maximum Post-Bronchodilator Method. Participants' reversibility will be assessed at Visit 1 (Screening). For participants unable to achieve ≥12% reversibility and 200 mL change at Visit 1, reversibility can be repeated at Visit 2 to confirm eligibility for the study (see randomisation criterion 2, Section 5.3.1). The procedures involved in the Maximum Post-Bronchodilator Method are those generated by the Asthma Clinical Research Network. Additional details on the reversibility testing procedures using the Maximum Post-Bronchodilator Method can be found in the spirometry section of the third-party vendor manual.

8.2.4. St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a well-established instrument, comprising 51 questions designed to measure Quality of Life in participants with diseases of airway obstruction [Jones, 1992]. The questionnaire will be administered as per guidance from the measure developers and completed electronically according to the SoA (Section 1.3).

8.2.5. Asthma Control Questionnaire-5 (ACQ-5)

The ACQ-5 is a five-item questionnaire, which has been developed as a measure of participants' asthma control that can be quickly and easily completed [Juniper, 2005]. The questions are designed to be self-completed by the participant. The five questions enquire about the frequency and/or severity of symptoms (nocturnal awakening on

waking in the morning, activity limitation, and shortness of breath, wheeze) over the previous week. The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. This will be completed electronically according to the SoA (Section 1.3).

8.2.6. PROMIS Fatigue Items

The PROMIS Fatigue Item Bank includes a number of items assessing concepts from mild tiredness to exhaustion [Christodoulou, 2008; Cella, 2016]. A small number of individual questions assessing the concept of "Energy" from the PROMIS Fatigue item bank will be administered. Participants will complete these items on an electronic handheld device.

The PROMIS fatigue items should only be administered to participants for whom an appropriate translation is available (see the SRM for further details).

8.2.7. Sino-nasal Outcomes Test-22 (SNOT-22)

The SNOT-22 is a 22-item self-administered questionnaire to measure disease-specific quality of life of chronic rhinosinusitis (with or without nasal polyposis). The SNOT-22 contains questions about a broad range of health and HRQoL problems including physical problems, functional limitations and emotional consequences. The questions are designed to be self-completed by the participant [Hopkins, 2009]. The participant is asked to rate the severity of each item over the previous 2 weeks on a scale from 0 (no problem) to 5 (problem as bad as it can be). Responses to the questionnaire will be captured electronically.

The SNOT-22 questionnaire should only be administered to participants for whom an appropriate translation is available (see the SRM for further details).

8.2.8. Patient Global Impression of Asthma Severity/Change (PGI-S, PGI-C)

Patient Global Impression of Asthma Severity (PGI-S): The participant will complete a PGI-S question at Randomisation and visits according to the SoA (Section 1.3). This single global question will ask participants to rate their asthma severity on a five-point scale (no symptoms, mild, moderate, severe, very severe). Responses will be captured electronically.

Patient Global Impression of Change (PGI-C) from Baseline of Asthma Severity: The participant will complete a PGI-C question from baseline of their asthma severity at the visits specified in the SoA (Section 1.3). The single question will ask participants to rate the overall change in their asthma severity compared with Day 1 (randomisation) prior to start of study intervention. The rating will use a five-point scale (much better, a little better, no change, a little worse, much worse) and responses will be captured electronically.

Additional instructions will be provided in the SRM.

8.2.9. Clinician/Patient Rated Response to Therapy

This is an overall evaluation of response to treatment, conducted separately by the investigator and the participant using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse

The evaluations will be completed electronically at the visits specified in the SoA (Section 1.3).

8.2.10. Asthma Daily Symptom Diary/Asthma Nightly Symptom Diary (ADSD/ANSD)

The ADSD/ANSD is a 6-item self-administered patient-reported diary developed by the PRO Consortium's Asthma Working Group (in accordance with the Food and Drug Administration's PRO Guidance) to facilitate comprehensive and reliable assessment of asthma symptoms from a patient's perspective [Gater, 2016].

The ADSD/ANSD is intended for use by adults and adolescents (aged 12 years and older) who are diagnosed with asthma to rate the severity of their symptoms in the three core categories: breathing symptoms (wheezing, shortness of breath), chest symptoms (chest tightness, chest pain) and cough.

The ADSD/ANSD must be completed twice daily by the participant:

- The morning diary (ADSD) is to be completed upon waking and refers to asthma symptoms during the night-time.
- The evening diary (ANSD) is to be completed before going to bed and refers to asthma symptoms during the day.

Participants are required to rate the six symptoms at their worst during the respective timeframes using an 11-point numeric rating scale (NRS) ranging from 0 ('None') to 10 ('As bad as you can imagine'). Responses will be captured electronically.

Further details are contained in the SRM.

8.2.11. eDiary Asthma Parameters and Alerts

The participant will be asked to record the following parameters daily in the eDiary from Visit 1 onwards:

- Morning peak expiratory flow (best of three), before rescue medication usage (L/min).
- Occasions of rescue usage over the previous 24-hours.

- Asthma symptom score over the previous 24-hours using a 6-point scale (Appendix 9).
- Frequency of awakening due to asthma symptoms requiring rescue medication use.

For safety the following alerts, indicative of worsening asthma, will be programmed into the eDiary with instructions to contact the investigator if any of the alert criteria are met. An alert in itself will not qualify as a clinically significant exacerbation:

- Decrease in morning PEF ≥30% on at least two of three successive days, compared with baseline (last 7 days of run-in).
- An increase of ≥50% in rescue medication on at least two of three successive days, compared with the average use for the previous week.
- Awakening due to asthma symptoms requiring rescue medication use for at least two of three successive nights.
- A symptom score of 5 for at least two of three successive days.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3) – where possible, these should be aligned with standard of care.

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Eyes, CV, Respiratory, Gastrointestinal and Neurological systems. Height (screening only) and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

- Oral or skin temperature, pulse rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the resting state with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and should be taken before blood collection for laboratory tests.

8.3.3. Electrocardiograms (ECGs)

- Twelve-lead ECGs will be obtained at the time points specified in the SoA (see Section 1.3) using an ECG machine, provided by GSK via a designated central laboratory, that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

- The QTcF formula must be used for *each* individual participant to determine eligibility. This formula may not be changed or substituted once the participant has been enrolled. Refer to Section 7.1.2 for the QTcF formula.
- If a routine ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTcF values of the three ECGs to determine whether the participant should be discontinued from the study intervention (but not from the study). Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- ECG measurements will be made after the participant has rested in the supine position for 5 minutes. The ECG should be obtained after the vital signs assessments but before lung function testing followed by other study procedures. Collection shortly after a meal or during sleep should be avoided since QT prolongation can occur at these times.
- Paper ECG traces will be recorded at a standard paper speed of 25 mm/sec and gain of 10 mm/mV, with a lead II rhythm strip. There will be electronic capture and storage of the data by a validated method.
- Paper ECG traces are required to be maintained at the site with other source documents.

8.3.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and refer to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study until the Exit Visit (or Follow-up visit/call if applicable) should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or Medical Monitor. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the Sponsor notified.
- If laboratory values from non-protocol specified laboratory tests performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

- To maintain the treatment blind, the site and the central study team will not be sent information on haematology differential (absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes) from any visits post-randomisation.

8.3.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- A serum pregnancy test should be conducted for all WOCBP at the screening visit (Visit 1) and the Exit visit. In addition, a urine pregnancy test should be performed for all WOCBP prior to randomisation (Visit 2), on a monthly basis at the specified scheduled study visit, and at the Follow-up Visit/call (if applicable) as per the SoA (Section 1.3).
- A final urine pregnancy test should be conducted for all WOCBP, 30 weeks after the last administered dose of study intervention:
    - Participants who enter the OLE study will have a urine pregnancy test prior to receiving the first dose of open-label GSK3511294.
    - Participants who do not enter the OLE study should have a urine pregnancy test at the Follow-up Visit/call (Week 56). A self-reported home urine pregnancy test result is acceptable if the follow-up is conducted as a phone call visit.
    - Participants who withdraw early from the study should have a urine pregnancy test, 4 weeks after the WS Visit (see Section 7.2).
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Section 10.3. Asthma exacerbations should not be recorded in the AE section of the eCRF unless they meet the definition of a SAE.

The definitions of device-related safety events, (adverse device effects [ADEs] and serious adverse device effects [SADEs]), can be found in Section 10.7. Device deficiencies are covered in Section 10.7.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of intervention (Visit 2) until the Exit Visit or follow-up visit/call (if applicable) at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the Exit Visit or the follow-up visit/call (if applicable) at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions (in the eCRF) not as AEs.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to GSK within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify GSK.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 8.4.7), will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to GSK of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from GSK will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and GSK policy and forwarded to investigators as necessary.

8.4.5. Pregnancy

- Any female participant who becomes pregnant while participating in the study will not receive another dose of study intervention.
- Details of all pregnancies in female participants will be collected from the start of study intervention and until 30 weeks after the last administered dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within **24 hours** of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.4.6. Cardiovascular and Death Events

For any CV events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV CRF pages are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific CV section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF page is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.4.7. Adverse Events of Special Interest

Adverse events of special interest (AESI) include:

- Allergic reactions including anaphylaxis

  Note: these events will be assessed by the investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006] (Appendix 8).

- Type III hypersensitivity (immune complex disease/vasculitis) reactions
- Local injection site reactions
- QTc prolongation

See Section 2.3.1 for additional details.

8.4.8. Medical Device Deficiencies

Medical devices (PFS) are being provided for use in this study as a delivery method for GSK3511294 or matching placebo injections. To fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device Deficiency can be found in Section 10.7.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 10.3 of the protocol.

8.4.8.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- The method of documenting Medical Device Incidents is provided in Section 10.7.

8.4.8.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study.

- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.8.3. Prompt Reporting of Medical Device Deficiencies to Sponsor

- Device deficiencies will be reported to the Sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.
- The Medical Device Deficiency Report Form will be sent to the Sponsor by email. If email is unavailable, then fax should be utilised.
- The Sponsor will be the contact for the receipt of device deficiency reports.

8.4.8.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all deficiencies occurring with any medical device provided for use in the study in order for the Sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.5. Pharmacokinetics

- Blood samples will be collected for measurement of plasma concentrations of GSK3511294 as specified in the SoA (Section 1.3).
- The actual date and time (24-hour clock time) of each sample will be recorded. Samples obtained at Visit 2 (Week 0) and Visit 10 (Week 26) should be drawn prior to dosing.
- Collection, processing, storage and shipping procedures are provided in the central laboratory manual.
- Intervention concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6. Genetics and Pharmacogenomics

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Section 10.5. Genetics and Pharmacogenomics for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the central laboratory manual.

8.7. Biomarkers/ Pharmacodynamic Markers

8.7.1. Blood Eosinophil Counts

In order to investigate the PD effects of GSK3511294, blood eosinophil counts will be measured as part of the standard haematological assessments according to the SoA (Section 1.3). The site staff and central study team will be blinded to each participant's blood eosinophil count (as well as overall haematology differential [absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes]) from all post-randomisation blood tests. Total white blood cell counts will be available throughout the study.

8.7.2. Complement, IgE, and Inflammatory Markers

Blood samples will be collected to measure complement (C3 and C4) and total IgE, according to the SoA (Section 1.3).

A baseline serum sample will be collected at Visit 2 and stored. If necessary, this sample may be analysed for the presence of ANCA (using anti-MPO antibody and anti-PR3 antibody tests), and ANA, including anti-dsDNA antibodies. After dosing, additional inflammatory markers and tests may be considered on an ad-hoc basis should there be clinical concerns regarding an immune-mediated AE (see Section 7.5).

8.7.3. Exploratory Biomarkers

With the participant's consent and where permitted, a serum sample for exploratory biomarkers will be collected as specified in the SoA (Section 1.3). The samples will be stored after collection and may be analysed for any biomarkers that are thought to play a role in GSK3511294 response, asthma or related diseases, or to evaluate their association with observed clinical responses to GSK3511294. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to GSK3511294.

Participation in exploratory biomarker research is optional. Participants who do not wish to participate in the exploratory biomarker research may still participate in the study.

8.8. Immunogenicity Assessments

Antibodies to GSK3511294 will be evaluated in serum samples collected from participants according to the SoA (Section 1.3). Additionally, serum samples should also

be collected at the Exit Visit or the final in-clinic visit for participants who withdraw early from the study. Processing, storage and shipping procedures are provided in the SRM.

In the immunogenicity assessment for GSK3511294, a tiered analyses approach will use a validated binding ADA assay (screening, confirmation and titration assays) and a validated neutralisation antibody (NAb) assay. If necessary, further immune response characterisation may be performed as needed.

8.9. Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation data, associated with medical encounters, will be collected by the investigator and study-site personnel for all participants throughout the study. The data will be collected using a medical problems and healthcare utilisation worksheet according to the SoA (Section 1.3). Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to evaluate the effect of GSK3511294 on health care resource utilisation for asthma including hospitalisation, ED visits, and physician office/clinic visits.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary study objective is to test for the superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC, assessed by the annualised rate of clinically significant exacerbations measured over the study intervention period of 52 weeks.

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 and placebo.

9.2. Sample Size Determination

Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125).

9.2.1. Sample Size Assumptions

A sample size of 375 participants (2:1 GSK3511294 to placebo allocation ratio) is based on sufficient power to conclude superiority on primary and key secondary endpoints.

9.2.1.1. Primary Endpoint

The assumed true annualised rate of exacerbations in the placebo arm is 1.18. Based on an assumed true treatment difference of a 50% reduction in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC, a sample size of 375 randomised participants (250 to GSK3511294, 125 to placebo) will provide 99% power for the primary endpoint at a 5% two-sided significance level [PASS, 2020].

The assumptions for the placebo rate and treatment effect are median values from an elicitation exercise which used Phase 3 anti-IL-5/5R historical data (~50% reduction in exacerbations) and expert opinion. The sample size is based also on an assumption of 0.8 for the dispersion parameter which was observed in two mepolizumab studies [Pavord, 2012; Ortega, 2014]. It was assumed that 14% of participant-years data will be missing due to study withdrawal, which is also consistent with mepolizumab studies.

Based on the assumptions above, the minimum observed treatment difference estimated to result in significance at the 5% two-sided significance level is a 27% reduction in exacerbations for GSK3511294 + SoC compared with placebo + SoC (rate ratio of 0.73).

9.2.1.2. Secondary Endpoints

Table 3 describes the assumptions and power values for two key secondary endpoints. The assumptions are obtained from the Phase 3 mepolizumab studies [Pavord, 2012; Ortega, 2014; Chupp, 2017].

Table 3 Power Calculations for Key Secondary Endpoints

Endpoint	Assumed treatment difference (GSK3511294 + SoC vs. placebo + SoC)	Standard deviation	Power
Change from baseline in SGRQ total score at Week 52	-7	17	96%
Change from baseline in ACQ-5 score at Week 52	-0.35	1.1	83%

9.2.2. Sample Size Sensitivity

The sample size and power calculations are based on assumptions about the true values for parameters. The power of the study is dependent on changes in these assumptions, in particular the assumed annualised exacerbation rates. Table 4 illustrates how changes in assumptions for two parameters (placebo + SoC annualised exacerbation rate and treatment effect) affect the power.

Table 4 Estimates of Power for Assumed Placebo + SoC Exacerbation Rate and Assumed Percent Reduction with GSK3511294 + SoC Compared with Placebo + SoC

Percent reduction in annualised exacerbation rate with GSK3511294 + SoC vs. placebo + SoC	Placebo + SoC annualised exacerbation rate			
	1.0	1.1	**1.18**	1.3
30%	61	63	65	67
40%	88	90	91	92
50%	98	99	**99**	99

9.3. Analysis Sets

For the purpose of analyses, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF and for whom a record exists.
Safety	All randomised participants who receive at least one dose of study intervention. Participants will be analysed according to the study intervention they actually received.
Modified Intent-to-Treat (mITT)	All randomised participants who receive at least one dose of study intervention. This population will serve as the primary population for

	analyses of efficacy endpoints and will utilise the actual intervention received.

All further populations to be used for the assessment of biomarker, PK, and health resource use will be defined in the SAP.

9.4. Statistical Analysis

The SAP will be finalised prior to un-blinding and it will include a more technical and detailed description of the statistical analyses described in this section.

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC.

9.4.2. Primary Endpoint

9.4.2.1. Main Estimand

Target Participant Population	Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.
Primary Endpoint	Annualised rate of clinically significant exacerbations over 52 weeks. Clinically significant exacerbations are defined in Section 8.2.2.
Intercurrent events and strategies	The anticipated key intercurrent events and corresponding strategies are: a) Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring b) Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred c) Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring
Summary measure	Ratio of the rates of exacerbations between GSK3511294 + SoC and placebo + SoC.
Analysis Method	The primary analysis of the annualised rate of clinically significant exacerbations will use a negative binomial model. Covariates included will be baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high dose, see Appendix 10), region, number of exacerbations in the year prior to the study, baseline % predicted FEV_1 and treatment group with

	log_e(time in study in years) as an offset variable. The rate ratio and 95% confidence interval (CI) will be provided for the comparison between GSK3511294 + SoC and placebo + SoC.
Handling of missing data and intercurrent events leading to exclusion of data	Missing data or data excluded due to intercurrent events will be handled as follows: • For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed "missing at random" (MAR) (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the primary endpoint, the data for the period following withdrawal will be assumed MAR (based on all data included in the analysis under the current estimand strategy). **Sensitivity analyses** will be conducted to investigate the conclusions from deviations from these assumptions regarding missing data for (b) above. Missing data for participants will be based on data from participants who have discontinued study intervention (off-treatment) but remained in the study [Roger, 2019]. A tipping point analysis will also be conducted that will impute missing data based on a plausible range of values for the rate of exacerbations per year. The imputed exacerbation rates will be varied independently for treatment arms. Further details will be provided in the SAP.

9.4.3. Secondary Endpoints

9.4.3.1. Main Estimands

Target Participant Population	Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.
Secondary Endpoints	• Change from baseline in SGRQ total score at Week 52 • Change from baseline in ACQ-5 score at Week 52 • Change from baseline in pre-bronchodilator FEV_1 at Week 52
Intercurrent events and strategies	The anticipated key intercurrent events and corresponding strategies: a) Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring. b) Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred. c) Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring

Summary measure	Difference in means between GSK3511294 + SoC and placebo + SoC.
Analysis Method	The analysis will be performed using a repeated measures mixed model. Covariates included will be baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high dose, see Appendix 10), number of exacerbations in the year prior to the study, baseline % predicted FEV_1,treatment group and visit, plus interaction terms for visit by baseline and visit by treatment group. The difference in means and 95% CI will be provided for the comparison between GSK3511294 + SoC and placebo + SoC.
Handling of missing data and intercurrent events leading to exclusion of data	Missing data or data excluded due to intercurrent events will be handled as follows: a) For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). b) For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy). **Sensitivity analyses** will be conducted to investigate the conclusions from deviations from these assumptions regarding missing and excluded data for (b) above. Missing data for participants will be based on data from participants who have discontinued study intervention (off-treatment) but remained in the study [Roger, 2019]. A tipping point analysis will also be conducted that will impute missing data based on a plausible range of means. The imputed means will be varied independently for treatment arms. Further details will be provided in the SAP.

The annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks will be evaluated using the same strategy as that described for the primary endpoint (see Section 9.4.2).

9.4.4. Other Endpoints

Full details of analysis methods to be used for other endpoints will be provided in the SAP.

9.4.5. Safety Analyses

All safety analyses will be performed on the Safety Population. Summaries of data will report data according to the nominal visit for which it was recorded. Occurrence of AEs, SAEs, AESIs, laboratory data, vital signs, and ECGs will be included in data displays in the form of listings, frequency tables, summary statistics, graphs, and statistical analyses where appropriate.

Adverse Events (AEs) will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and will be grouped by system organ class (SOC). AEs

will be summarised by frequency and percentage of participants, by SOC and preferred term within each treatment group. Separate summaries will be presented for all AEs, drug-related AEs, serious AEs (SAEs), AEs leading to permanent discontinuation of study intervention or withdrawal from study and for any AEs of special interest.

9.5. Multiple Testing Strategy

The treatment comparison of interest for the primary and secondary endpoints is GSK3511294 100 mg SC + SoC vs placebo + SoC. A fixed sequence hierarchical testing procedure will be used to provide strong control of Type I error for multiplicity arising from the primary and multiple secondary endpoints. This will be carried out using a stepdown closed testing procedure where inference for an endpoint in the predefined hierarchy will be dependent on statistical significance having been achieved for the previous endpoints in the hierarchy. For example, for the primary endpoint, GSK3511294 + SoC will be compared to placebo + SoC at a two-sided 5% level. The next endpoint in the hierarchy (i.e. the first secondary endpoint) will be tested only if the test for the primary endpoint is significant at the two-sided 5% level. Testing will continue down the hierarchy for the remaining endpoints in an equivalent manner only if the previous endpoint in the hierarchy achieves statistical significance.

The hierarchy of the primary and secondary endpoints to be tested is as follows:

1. Annualised rate of clinically significant exacerbations over 52 weeks
2. Change from baseline in SGRQ at Week 52
3. Change from baseline in ACQ-5 at Week 52
4. Change from baseline in clinic pre-bronchodilator FEV_1 at Week 52
5. Annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

9.6. Interim Analysis

No interim analyses are planned.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide GSK with sufficient, accurate financial information as requested to allow GSK to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or their legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- For participants 12-17 years old, written informed assent must be obtained in addition to the legally authorised representative(s)' consent. Assent will be obtained in accordance with applicable country or IRB/Ethics Committee regulations. Written informed consent will be obtained from participants turning 18 years of age to continue participation in the study.
- The medical record must include a statement that written informed consent/assent was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorised person obtaining the informed consent/assent must also sign the ICF.
- Participants must be re-consented/re-assented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorised representative.

Participants who are rescreened are required to provide consent/assent and sign a new ICF/assent form.

GSK (alone or working with others) may use a participant’s coded study data and samples and other information to carry out this study; understand the results of this study; learn more about GSK3511294 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have GSK3511294 approved for medical use or approved for payment coverage.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by GSK. Any participant records or datasets that are transferred to GSK will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by GSK in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by

GSK, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

An Independent Data Monitoring Committee (IDMC) comprised of clinical experts external to GSK will review unblinded data at defined timepoints during the study. If deemed appropriate by the IDMC, or upon request by GSK or investigators, additional timepoints for review may be added.

Details of the structure and function of the IDMC, and analysis plan for IDMC reviews, are outlined in the IDMC Charter, which is available upon request.

In addition to the IDMC, the GSK SRT will review blinded safety data at regular intervals throughout the study to ensure participant safety, which includes safety signal detection at any time during the study. Details of the SRT process will be available in relevant SRT documents. The SRT will inform the IDMC if any safety signals are identified.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymised participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymised patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- GSK or a designee is responsible for the data management of this study including quality checking of the data.
- GSK assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of GSK. No records may be transferred to another location or party without written notification to GSK.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records

or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or

suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- GSK will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, GSK will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

All protocol required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).

Local laboratory results may be required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation to be performed – for example: when results from screening Visit 1 should be available before dosing on Visit 2, or at any time when a participant is unwell and results are required urgently.

If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded in the CRF.

To maintain the blind, the following data for post-randomisation samples will not be reported to investigators and blinded Sponsor representatives: absolute and percentage values of eosinophils, neutrophils, lymphocytes, monocytes, and basophils.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	**Parameters**			
Haematology[1]	Platelet Count	*RBC Indices:*	*WBC count with Differential: (post-dose results blinded as described in footnote 1)*	
	RBC Count	MCV	WBC	
	Haemoglobin	MCH	Neutrophils	
	Haematocrit	%Reticulocytes	Lymphocytes	
			Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry[2]	BUN	Potassium	AST(SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase[3]	Albumin
		Magnesium		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination and UACR (if blood or protein is abnormal [evidence of microalbuminuria or haematuria of ≥1+])			
Pregnancy testing	• Highly sensitive serum pregnancy test at Screening Visit 1 and Exit Visit; urine pregnancy tests for all other scheduled visits (as needed for WOCBP)[4]			
Other Screening Tests	• FSH and oestradiol (if required to confirm postmenopausal status) • Parasitic Screening (only required in regions with high-risk or for participants who have visited high-risk regions in the past 6 months). Sites should use local laboratories. • Total IgE • Serum samples collected at baseline will be frozen and stored for later analyses, if necessary: anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			

NOTES:
ALT = Alanine Aminotransferase; ANA = anti-nuclear antibody; AST = Aspartate Aminotransferase; BUN = Blood urea nitrogen; FSH = Follicle-stimulating hormone; MPO=myeloperoxidase; PR3=proteinase 3; SGOT = Serum Glutamic-Oxaloacetic Transaminase; SGPT = Serum Glutamic-Pyruvic Transaminase; UACR = urinary albumin-creatinine ratio; WBC = white blood cell; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

1. To maintain the treatment blind, the following data for post-randomisation samples will not be reported to investigators and blinded Sponsor representatives: absolute and percentage values of eosinophils, neutrophils, lymphocytes, monocytes, and basophils.
2. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.6 All events of ALT ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalised ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported to GSK as an SAE.
3. If alkaline phosphatase is elevated, consider fractionating.
4. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention.

  NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalisation for signs/symptoms of the disease under study, death due to progression of disease, etc.).

An SAE is defined as any serious adverse event that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation

• In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AE. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalised ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias

- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours and send/fax it to the Medical Monitor. • The site will enter the SAE data into the electronic system as soon as it becomes available. • The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to study intervention/study participation (causality) within 72 hours of SAE entry into the eCRF. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor or the SAE coordinator by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Medical monitor or the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.
- Permanent sterilisation methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female
   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   a) A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   b) Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance:

Female participants:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)c
• Bilateral tubal occlusion
• Azoospermic partner (vasectomised or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

• Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulationc
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulationc
  • oral
  • injectable

• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

Male participants: As GSK3511294 is a mAb that is not anticipated to interact directly with deoxyribonucleic acid (DNA) or other chromosomal material and minimal exposure through semen is expected, male participants will not be required to use contraception during the study.

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK3511294 or asthma with an eosinophilic phenotype and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3511294 or study interventions of this drug class, and indication. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- Additional analyses of DNA samples may be conducted if it is hypothesised that this may help further understand the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to GSK3511294 or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3511294 (or study interventions of this class) or asthma with an eosinophilic phenotype continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Required Actions, Monitoring and Follow-up Assessments

Liver Chemistry Stopping Criteria and Increased Monitoring Criteria are designed to assure participant safety and evaluate liver event aetiology.

Liver Chemistry Stopping criteria and Required Follow-up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** total bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5
Cannot Monitor	ALT ≥ 5xULN but <8xULN **and** cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN **and** cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions, Monitoring and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study intervention • Report the event to GSK **within 24 hours** • Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform follow-up assessments as described in the Follow-up Assessment column. • Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below) **MONITORING:** **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5:**	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis, within a week of meeting increased liver monitoring criteria.[5] • Obtain a serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin. • Fractionate bilirubin, if total bilirubin≥2xULN

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **For all other stopping criteria (total bilirubin <2xULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilise or return to within baseline **RESTART/RECHALLENGE** • **Do not restart/rechallenge** participant with study intervention since **it is not allowed per protocol;** continue participant in the study for any protocol specified follow-up assessments.	• Obtain complete blood count with differential to assess eosinophilia. This blood sample will be sent to the central laboratory to maintain the blind while study is ongoing. Results will be provided only if unblinding of a participant's treatment assignment is required. Also note that the mechanism of action of GSK3511294 leads to lowering of eosinophils. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications. • Record alcohol use on the liver event alcohol intake form **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease; complete Liver Imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance:

	○ In patients when serology raises the possibility of autoimmune hepatitis (AIH) ○ In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention ○ In patients with acute or chronic atypical presentation: • If liver biopsy conducted complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3xULN and total bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5 which may indicate severe liver injury (possible 'Hy's Law'), **must be reported to GSK as an SAE**; the INR threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: hepatitis A Immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal, 2005].
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the central laboratory manual.

Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** total bilirubin <2xULN or INR≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** total bilirubin <2xULN or INR≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) until they resolve, stabilise or return to within baseline. • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, (total bilirubin <2xULN and INR ≤1.5) continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and total bilirubin <2xULN and INR ≤1.5, monitor participants twice monthly until liver chemistries resolve or return to within baseline.

References

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

10.7. Appendix 7: AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the Sponsor will comply with all local medical device reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.1.1 for the list of GSK medical devices).

10.7.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• An AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. • An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term ‘life-threatening' in the definition of ‘serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function.

• Inpatient or prolonged hospitalisation. Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to foetal distress, foetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.7.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

10.7.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- Other measures to evaluate AEs and SAEs may be utilised (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/device deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.7.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor or the SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool

- Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the Medical Monitor or the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

10.7.6. Reporting of SADEs

SADE Reporting to GSK

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

10.8. Appendix 8: Anaphylaxis Criteria

Joint National Institute of Allergy and Infectious Disease (NIAID)/ Food Allergy and Anaphylaxis Network (FAAN) Second Symposium on Anaphylaxis [Sampson, 2006]. The criteria do not make a distinction based on underlying mechanism. These criteria are summarised as follows:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalised hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
    a) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a) Involvement of the skin-mucosal tissue (e.g., generalised hives, itch-flush, swollen lips-tongue-uvula)
    b) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a) Adolescents (aged 12-17): low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

10.9. Appendix 9: Daily Asthma Symptom Score

Each morning, participants will record an asthma symptom score using the following scale:

Daily Symptom Score:

- 0 = No symptoms during the previous 24-hours.
- 1 = Symptoms for one short period during the previous 24-hours.
- 2 = Symptoms for two or more short periods during the previous 24-hours.
- 3 = Symptoms for most of the previous 24-hours which did not affect my normal daily activities.
- 4 = Symptoms for most of the previous 24-hours which did affect my normal daily activities.
- 5 = Symptoms so severe that I could not go to work/school or perform normal daily activities.

10.10. Appendix 10: Low, Medium and High Daily Doses of Inhaled Corticosteroids

Daily medium and high dose ICS options for adults and adolescents (12 years and older) are shown in Figure 1.

Figure 1 Low, medium and high daily doses of inhaled corticosteroids

Box 3-6. Low, medium and high daily doses of inhaled corticosteroids

This is not a table of equivalence, but instead, suggested total daily doses for the 'low', 'medium' and 'high' dose ICS options for adults/adolescents, p.54 and children 6–11 years, p.55, based on available studies and product information. Data on comparative potency are not readily available and therefore this table does NOT imply potency equivalence. Doses may be country-specific depending on local availability, regulatory labelling and clinical guidelines.

Low dose ICS provides most of the clinical benefit of ICS for most patients with asthma. However, ICS responsiveness varies between patients, so some patients may need **medium dose ICS** if their asthma is uncontrolled despite good adherence and correct technique with low dose ICS (with or without LABA). **High dose ICS** (in combination with LABA or separately) is needed by very few patients, and its long-term use is associated with an increased risk of local and systemic side-effects, which must be balanced against the potential benefits.

Inhaled corticosteroid	Total daily ICS dose (mcg) – see notes above		
	Low	Medium	High
Adults and adolescents (12 years and older)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (pMDI, extrafine particle*, HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle*, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	200		400
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400
Children 6–11 years – see notes above (for children 5 years and younger, see Box 6-6, p.153)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle*, HFA)	50-100	>100-200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80-160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50-100	>100-200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50-100	>100-200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; n.a. not applicable; pMDI: pressurized metered dose inhaler (non-chlorofluorocarbon formulations); ICS by pMDI should preferably be used with a spacer. *See product information.

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10.11. Appendix 11: Recommended Measures Related to COVID-19 Pandemic

Overall Rationale for this Appendix:

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the study intervention or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the study intervention or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

STUDY PROCEDURES DURING COVID-19 PANDEMIC

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrolment and treatment decisions for trial participants.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants.

- Clinical investigators should document in site files and in participant notes/Electronic Heath Records as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).

- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

- Spirometry should not be conducted for participants with confirmed/suspected COVID-19.

Protocol Defined Procedures/Visits:

- Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, measurement of vital signs and weight, and preparation and administration of study drug (at the discretion of the investigator). It is the

responsibility of the investigator to inform GSK when this occurs and to document in source notes.

- Remote visits may be performed at the participant's home by qualified study personnel or at a local medical facility, unless the investigator deems that a site visit is necessary.
- Additional unscheduled safety assessments such as routine blood sampling may be performed at the discretion of the investigator including in the participant's home, if deemed necessary. Biological samples may be collected at a different location, other than the study site (e.g., at participant's home) by qualified study personnel or at a local medical facility according to standard operating procedures and applicable regulations (see note). Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If visits to a site/home are not feasible, then the medical evaluation of the participant's asthma may take place by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress. GSK will be accountable for working with the vendor to ensure the site has the required equipment, training and support for this model and should be notified as soon as possible by the investigator that the service is required.
- The study investigator is responsible for ensuring that the identification, management, and reporting of AEs and SAEs are completed in accordance with the protocol and applicable regulations. AEs are first reported by participants to the investigator/study team or may be identified by the study team during interactions with the participants via telemedicine encounters. In addition, mobile nurses may identify AEs as well and report them to the investigator for evaluation. Additionally, AEs may be identified from lab reports, imaging or ECG reports, and other records. As determined by the investigator, the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary.
- The participant should be informed of the plan and any potential risks associated with the virtual medium and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.
- The revised schedule of study activities is provided in Table 6.

Note: If the investigator wishes to conduct a trial visit at a location that has not been previously assessed by GSK, it is the investigator's responsibility to identify an adequate alternate location and to notify GSK of the alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, is well-equipped to perform study procedures and covered by an adequate insurance. Furthermore, the investigator should have sufficient oversight to ensure that the staff at the alternate location are trained to perform study procedures. Refer to and follow most recent local guidance and regulations if available or refer to FDA or EMA guidance available at time.

Study Intervention:

- If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (see Section 6 Study Intervention and Concomitant Therapy), a maximum dose interval of 28 weeks may be used.
- In-clinic visits are required for administration of the study intervention (Week 0 and Week 26).
- In some cases, trial participants who no longer have access to study intervention or the investigational site may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment).

Data Management/Monitoring:

- The medical problems and healthcare utilisation worksheet may be transmitted from and to the investigator by electronic mail and or conventional mail. If copies/scans of the paper worksheet are sent to the investigator by electronic mail, the participant should be instructed to maintain the original documents and to return them to the site when a visit to the site will be allowed.
- If the eDiary device was provided to the participant, it may be returned to the site by conventional mail after the end of the relevant data collection period (Visit 17 Exit Visit).
- If on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a patient and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.
- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilised during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK.

Assessments that can be Conducted Outside Clinical Study Site:

Activities/assessments that may be conducted outside of a clinical study site are indicated in Table 6.

- White boxes represent activities/assessments that are to be done during visits to the clinical study centre (pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 10, Exit Visit 17, and WS Visit if applicable).
- Grey boxes represent activities/assessments during study visits (Visits 3-9, Visits 11-16, and the FU Visit) that may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow (at the discretion of the investigator, based on safety and tolerability).
- The FU Visit may be conducted as a remote/home visit or as a phone call.
- During home visits, the scheduled collection of samples for laboratory and other assessments may be performed by a home healthcare professional.

Table 6 Schedule of Activities (SoA) Indicating Assessments that may be Conducted Outside of a Clinical Study Site

Protocol Activity	Pre-Screening	Screening /Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
General Eligibility Assessments																					
Informed consent [a]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote a.
Genetic sample informed consent [d]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote d.
Demography and childbearing status	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; All females must be assessed at Visit 1 to determine childbearing potential.
Inclusion/Exclusion criteria	X	X																			
Historical blood eosinophil count		X																			See footnote e.
Medical history		X																			Include cardiovascular (CV), CV risk factors, asthma, exacerbations, vasculitis, allergies and anaphylaxis.
Smoking status		X																			
Parasite screening		X																			Only required in regions with high-risk or for participants who have visited a high-risk region in the past 6 months. Use local laboratories for this test.
eDiary registration and training		X																			Conduct thorough eDiary training at Screening Visit 1 and throughout the study on as-needed basis.
Randomisation criteria			X																		Assess prior to randomisation; see footnote e.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Efficacy Assessments																					
Review for exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Spirometry (pre- and post-bronchodilator FEV_1)		X	X								X							X	X		FEV_1=Forced expiratory volume in 1 second; Spirometry should not be conducted for participants with confirmed/suspected COVID-19 (see Section 8.2.3).
ACQ-5			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		ACQ-5=Asthma Control Questionnaire-5
Review eDiary (asthma symptoms, PEF summary)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PEF=Peak expiratory flow
HRQoL: PRO and Health Outcomes Assessments																					
SGRQ			X		X		X				X				X			X	X		SGRQ=St. George's Respiratory Questionnaire
PROMIS (fatigue items)			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PROMIS= Patient-reported outcomes measurement information system
SNOT-22			X								X							X	X		SNOT-22=Sino-nasal Outcomes Test-22 Questionnaire
Complete ADSD/ANSD		←========= daily =========→							X	X	X	X	X	X	X	X	X	X			ADSD/ANSD=Asthma Daily/Nightly Symptom Diary; To be completed daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.
Clinician-rated response to therapy							X				X				X			X	X		
Patient-rated response to therapy							X				X				X			X	X		

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0** [a]	**Visit 1** [a]	**V2**[b] **R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS**[c]	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
PGI-S		X	X				X		X		X				X			X	X		PGI-S: Patient Global Impression of Severity (of asthma)
PGI-C							X		X		X				X			X	X		PGI-C: Patient Global Impression of Change (from baseline of asthma severity)
Safety Assessments																					
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Ensure maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications are reviewed.
Physical Examination		X																X	X		Include height and weight for the complete physical exam at Screening Visit 1. Height can be omitted for subsequent visits.
Vital Signs		X	X			X			X		X	X			X		X	X	X		
12-lead ECG		X	X								X							X	X		
AE/SAE Assessment	X [g]	X [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE=Adverse events; SAE=Serious adverse events; see footnote g.
Laboratory Assessments																					
Haematology with differential [f]		X [e]	X	X	X	X	X		X		X	X	X		X		X	X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing; see footnotes e and f.
Total IgE			X																		
Clinical Chemistry		X	X		X	X	X		X		X	X			X			X	X		Include liver chemistry.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Pregnancy Test (WOCBP only)		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	Serum pregnancy test should be done at screening Visit 1 and Exit Visit; urine pregnancy tests should be done for all other assessments; WOCBP=Women of childbearing potential; See Section 8.3.5 for additional information.
Urinalysis		X	(X)								X							X	X		Conduct at Visit 2 if not completed at Visit 1. Note: dipstick, send for analysis if abnormality is identified by dipstick
Anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			X																		ANA=antinuclear antibodies; MPO=myeloperoxidase; PR3=proteinase 3. Collected baseline sample will be stored and may be tested if necessary (see Section 7.5).
Complement C3 and C4			X				X				X				X			X	X		
PK sample			X	X	X	X	X		X		X	X	X		X			X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing.
Immunogenicity sample			X	X	X	X	X				X	X	X	X	X			X	X		
Blood biomarker sample			X				X				X				X			X			Sample will be stored and may be analysed for exploratory biomarkers (see Section 8.7.3)
Genetics sample			←========== The genetics sample can be collected at Visit 2 or any visit after ==========→																		See footnote d.

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Study intervention																					
Administer study intervention			X								X										Study intervention will only be administered in the clinic. Any scheduled assessments or sample draws should be performed beforehand. Monitor participant for at least 2h after administration (see Section 6.5).
eCRF/worksheets/other																					
Dispense Rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Register Visit in the IRT system	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	IRT=interactive response technology
Provide worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				The worksheet is a medical problems and healthcare utilisation worksheet.
Review worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
eDiary close out																		X	X		
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		eCRF=electronic Case Report Form

Protocol Activity	**Pre-Screening**	**Screening /Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -1**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -7	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	

a. Informed Consent must be obtained prior to initiating any study assessments. Pre-screening Visit 0 can occur any time from 0 to 14 days before Screening Visit 1.
b. Randomisation Visit 2 is 1 week after Screening Visit 1 but can be extended to up to 6 weeks after Visit 1 if, for example, a participant has an exacerbation during the run-in period. Results from Screening Visit 1 procedures must be available for review of randomisation criteria.
c. If a participant withdraws from the study, then the Withdraw from Study (WS) Visit should be conducted 26 weeks after the last administered dose of study intervention, i.e., at Week 26 if the second dose of study intervention was not received, or at Week 52 if the second dose of study intervention was received. A follow-up visit/call should also be conducted 30 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing.
d. Informed Consent for optional genetics research must be obtained before collecting a sample.
e. To be randomised, participants without a historical blood eosinophil count of ≥300 cells/µL in the 12 months prior to Screening Visit 1, must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1.
f. For haematology samples collected after Randomisation, the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will not be reported to site staff and Sponsor (to maintain the treatment blind). However, sites will be sent total white blood counts throughout the study. Samples should be taken prior to dosing at Week 0 and Week 26 visits.
g. SAEs must be collected from signing of Informed Consent if considered related to study procedures.

10.12. Appendix 12: Country-specific requirements

No country-specific requirements exist.

10.13. Appendix 13: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine transaminase
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibody
ADE	Adverse device events
ADSD	Asthma Daily Symptom Diary
ANSD	Asthma Nightly Symptom Diary
Anti-HBc	Hepatitis B core antibody
Anti-IL-5	Anti-Interleukin-5
Anti-IL-5R	Anti-Interleukin-5 receptor
AST	Aspartate aminotransferase
BiPAP	Bilevel positive airway pressure
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
cm	Centimetre
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Continuous positive airway pressure
CPK	Creatine phosphokinase
CRF	Case report form
CS	Corticosteroid
CSR	Clinical study report
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
ECG	Electrocardiogram
ED	Emergency department
eDiary	Electronic diary
EDTA	Ethylenediaminetetraacetic acid or disodium edetate
EGPA	Eosinophilic granulomatosis with polyangiitis
FAAN	Food Allergy and Anaphylaxis Network
FEV_1	Forced expiratory volume in 1 second
FP	Fluticasone propionate
FSH	Follicle stimulating hormone
FTIH	First Time in Humans
FVC	Forced vital capacity

g	Grams
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma glutamyl transferase
GINA	Global Initiative for Asthma
GLDH	Glutamate dehydrogenase
GSK	GlaxoSmithKline
h	Hours
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HFA	Hydrofluoroalkane product
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IFU	Instruction for use
Ig	Immunoglobulin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IM	Intramuscular
IMP	Investigational medicinal product
INR	International normalised ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
kg	kilogram
L	Litre
LA	Long-acting
LABA	Long-acting β-agonist
LAM	Lactational amenorrhea method
LAMA	Long-acting muscarinic antagonist
LDH	Lactate dehydrogenase
LTRA	Leukotriene receptor antagonist
mAb	Monoclonal antibody
MAR	Missing at random
mcg (μg)	Microgram

MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Millilitres
mm Hg	Millimetre of mercury
mol	Mole
MPO	myeloperoxidase
MSDS	Material Safety Data Sheet
msec	Milliseconds
NAb	Neutralising antibody
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NIMP	Non-investigational medicinal product
OCS	Oral corticosteroid
OLE	Open-label extension
PC_{20}	Provocative concentration causing a 20% fall in FEV_1
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PD_{20}	Provocative dose that decreases FEV_1 by 20%
PEF	Peak expiratory flow
PFS	Pre-filled safety syringe
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PR3	Proteinase 3
PRO	Patient-reported outcomes
PROMIS	Patient-reported outcomes measurement information system
QTcF	QTc corrected by Fridericia's formula
QTL	Quality tolerance limits
R&D	Research and Development
RNA	Ribonucleic acid
RBC	Red blood cell
SABA	Short-acting β-agonist
SADE	Serious adverse device event
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SGPT	Serum glutamic pyruvic transaminase
SGOT	Serum glutamic oxaloacetic transaminase
SGRQ	St. George's Respiratory Questionnaire
SNOT	Sino-nasal Outcomes Test
SoA	Schedule of assessments
SoC	Standard of care

SOC	System organ class
SRM	Study Reference Manual
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
UACR	Urinary albumin-creatinine ratio
UK	United Kingdom
ULN	Upper Limit of Normal
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential
w/v	Weight/volume
µL	Microlitre

Trademark Information

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Trademarks not owned by the GlaxoSmithKline group of companies
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CINQAIR
DUPIXENT
FASENRA
MedDRA
SAS
XOLAIR

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TITLE PAGE

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Protocol Number: 213744 /Amendment 02

Compound Number or Name: GSK3511294

Brief Title: Placebo-controlled efficacy and safety study of GSK3511294 (depemokimab) in participants with severe asthma with an eosinophilic phenotype

Study Phase: Phase 3A

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
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Medical Monitor Name and Contact Information can be found in the Study Reference Manual (SRM).

Sponsor Signatory:

David Lipson

Vice President and Disease Area Lead, Respiratory

Manufacturer: GlaxoSmithKline

Regulatory Agency Identifying Number(s):

IND: 146742

EudraCT: 2020-003611-10

Approval Date: 05 Apr 2022

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Number**
Amendment 02	*05* **Apr 2022**	TMF-14449506
Amendment 01	*17-Aug-2021*	TMF-13331276
Original Protocol	*01-Oct-2020*	TMF-2125388 (2020N439962_00)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Amendment 02: 05 Apr 2022

Overall Rationale for the Amendment:

Amendment 02 is a global amendment to include details about controlled early access to unblinded pharmacokinetics (PK) and pharmacokinetics pharmacodynamics (PKPD) data and futility analysis. Additional changes include repeated spirometry assessment and/or additional lab test if randomisation criteria are not met during screening, change in the ratio of medium/high ICS dose, allowance/permittance of authorized COVID-19 treatments, Global Initiative for Asthma (GINA) inhaled corticosteroid (ICS) doses update, and QT prolongation clarifications.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA)	Added new footnote “h” spirometry retest allowed during the run in period if a patient fails the protocol-specified reversibility criterion or FEV_1 inclusion criteria	To add flexibility in screening tests; current information suggests this change is expected to result in improved screening while maintaining the integrity of the patient population
	Added text to clarify that pregnancy text should be done at screening Visit 1 and Exit Visit/Withdraw from study visit	Clarification
	Updated text in footnote “e” the Screening Visit laboratory assessment can be repeated during the run in period if a patient does not meet the blood eosinophil count eligibility criteria at the Screening Visit test result	To add flexibility in screening tests; current information suggests this change is expected to result in improved screening while maintaining the integrity of the patient population

Section # and Name	Description of Change	Brief Rationale
	Added text to clarify that, electrocardiogram (ECG) must be performed and assessed pre-dose Added text to clarify that 12-lead ECG central over-read values should be used at all visits with the exception of Visit 2 and Visit 10 where 12-lead ECG machine read values should be used	Clarification Clarification
Section 2.3.1 Risk Assessment (QTc prolongation)	Removed text related to post-baseline QTcF value of potential clinical importance from first time in human (FTIH) study (205722) Updated text related to ECG parameters including corrected QT interval using Fridericia's formula (QTcF) for depemokimab treatment groups in the FTIH study (205722) Updated wordings related to analysis of the relationship between depemokimab plasma concentrations and change from baseline QTcF data collected in FTIH 205722 study	Modified text related to ECG parameters in the FTIH study (205722) for better clarity. No new safety information.
Section 4.1 Overall Design Section 6.4.1 Treatment Assignment	Changed the ratio of medium/high ICS dose from 25% medium ICS dose and 75% high ICS dose to aiming up to 50% approximately of participants on medium ICS dose	To better reflect dosing in clinical practice while maintaining the integrity of the patient population
Section 5.2 Exclusion Criteria (Prior/Concomitant therapy)	Text added in exclusion criteria no. 12 to clarify that Authorized monoclonal antibodies (mAbs) treatments for COVID-19 are permitted	Allowance of treatments for COVID-19 is not expected to impact the overall interpretability of the data generated from this study or lead to any safety concern with concomitant use of IMP
Section 5.2 Exclusion Criteria (Diagnostic Assesments)	Text added in exclusion criteria no.15 to clarify that the 12-lead	Clarification

Section # and Name	Description of Change	Brief Rationale
	ECG central over-read QTcF value is to be used	
Section 5.3.2 Randomisation Exclusion Criteria	Text added in randomisation exclusion criteria no. 3 to clarify that the 12-lead ECG machine read QTcF value is to be used at Visit 2. The central over-read of the Screening Visit 1 12-lead ECG should be used to review ECG findings at Visit 2.	Clarification
Section 6.4.3 Controlled Early Access to Unblinded PK and PKPD Data	Added sub section and included text regarding controlled early access to Unblinded PK and PKPD Data to designated independent representative(s)	Allow for development of PK/PD models and expedited reporting
Section 6.9.1 Permitted Medications and Non-Drug Therapies	"Additional asthma medications such as theophyllines and anti-leukotrienes will be permitted **as maintenance** provided that they have been taken regularly in the 3 months prior to screening (Visit 1)". Removed repeated wordings about vaccination against SARS-CoV-2 infection using authorized COVID-19 vaccines Text added to clarify that participants can be treated for SARS-CoV-2 infection using authorized COVID-19 treatments (including mAbs) in line with local/national guidelines. Experimental COVID-19 treatments are not permitted	Clarification Repeated text removed Allowance of treatments for COVID-19 is not expected to impact the overall interpretability of the data generated from this study or lead to any safety concern with concomitant use of IMP
Section 7.1.2 QTc Stopping Criteria	Text added to clarify that the QTcF value from the 12-lead ECG central over-read at randomisation Visit 2 should be used as baseline QTcF value for any changes from baseline calculations during the study	Clarification

Section # and Name	Description of Change	Brief Rationale
	Text added to clarify that after randomisation 12-lead ECG central over-read values should be used to assess QTc stopping criteria, with the exception of Visit 10 (Week 26) where 12-lead ECG machine read values should be used	Clarification
Section 8.1.2 Critical Assessment performed at Screening (Visit 1)	Added new text to clarify that if the Screening Visit test result does not meet the blood eosinophil count eligibility criteria, the laboratory assessment may be repeated, at the discretion of the investigator Added text for spirometry to clarify that if a patient fails the protocol-specified reversibility criterion or FEV1 inclusion criteria, spirometry restest is allowed during the run-in period	To add flexibility in screening tests; current information suggests this change is expected to result in improved screening while maintaining the integrity of the patient population To add flexibility in screening tests; current information suggests this change is expected to result in improved screening while maintaining the integrity of the patient population
Section 8.3.3 Electrocardiograms (ECGs)	Updated text related to additional ECGs to be performed if an ECG demonstrates a prolonged QTcF interval	Revised wording for clarification
Section 9.3 Analysis Sets	Updated text related to screened, enrolled, randomised, full analysis set, and safety population	Revised description of Analysis sets
Section 9.4.5 Safety Analyses	Safety population used for Safety analyses instead of mITT	To provide clarification that all safety analyses will be performed on the Safety Population
Section 9.6 Interim Analysis	Text deleted “no interim analyses are planned” Added text that an unblinded interim analysis for futility will be performed	Text removed to align with new interim analysis Futility analysis conducted to further evaluate benefit/risk
10.7.4 Recording and Follow-up of AE and/or SAE and Device Deficiencies (Assessment of Intensity)	Text deleted “other measures to evaluate AEs and SAEs may be utilised”.	Clarification

Section # and Name	Description of Change	Brief Rationale
Appendix 10 Medium and High Daily Doses of Inhaled Corticosteroids	Footnote added to clarify GINA 2021 guidelines updates	Update as per GINA 2021 guidelines
Section 11 References	Added and updated the reference	Updated the references
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Brief Title: Placebo-controlled efficacy and safety study of GSK3511294 (depemokimab) in participants with severe asthma with an eosinophilic phenotype

Rationale:

GSK3511294 is being developed as a long-acting (LA) subcutaneous (SC) injectable anti-interleukin-5 (anti-IL-5) therapy and is expected to deliver an efficacy and safety profile similar to current anti-IL-5 therapies with a reduced dosing frequency (once every 26 weeks). The aim of this study is to investigate the efficacy and safety, over a 52-week treatment period, of GSK3511294 100 mg SC given once every 26 weeks as adjunctive therapy in participants with uncontrolled severe asthma with an eosinophilic phenotype.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

Overall Design:

This study employs a multi-centre, randomised, placebo-controlled, double-blind, parallel group design to assess the efficacy and safety of GSK3511294 in participants with severe uncontrolled asthma with an eosinophilic phenotype despite standard of care (SoC) treatment with medium to high dose inhaled corticosteroid (ICS) plus at least one additional controller. All participants will receive study intervention as an adjunct therapy while remaining on their existing asthma therapy throughout the study.

Brief Summary:

The purpose of this study is to assess the efficacy and safety of GSK3511294 as an adjunctive therapy in participants with severe uncontrolled asthma with an eosinophilic phenotype. During the 52-week treatment period, participants will receive two doses (at Week 0 and Week 26) of add-on study intervention (GSK3511294 100 mg or matching placebo) by SC injection, while remaining on their existing maintenance asthma therapy (that excludes biologics) throughout the study. Assessments will include the annualised rate of clinically significant exacerbations and measures of lung function, asthma control, and safety.

Number of Participants:

Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125).

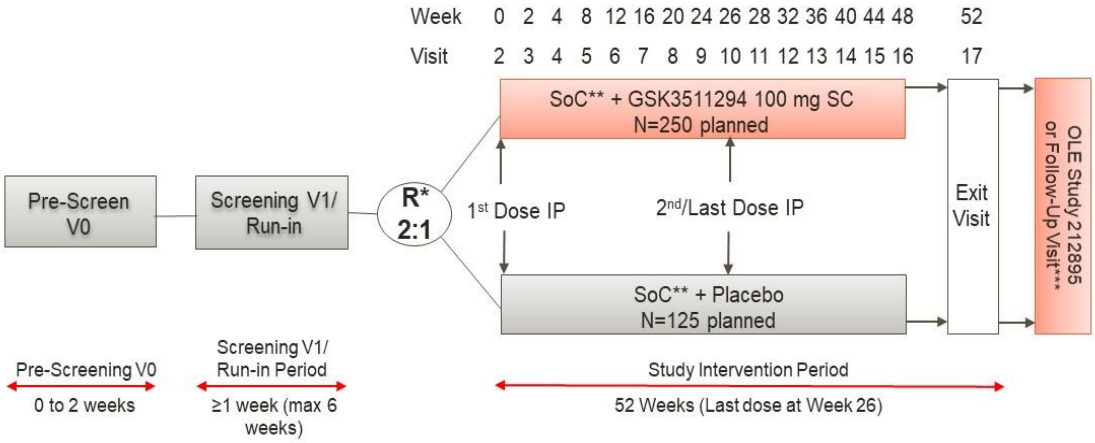
Intervention Groups and Duration:

The study will consist of a pre-screen period (0-2 weeks), a run-in period (1-6 weeks), and a study intervention period (52 weeks). After the run-in period, participants will be randomised in a 2:1 ratio using an interactive response technology (IRT) system in a blinded manner to receive either GSK3511294 100 mg or placebo by SC injection. Randomisation will be stratified based on baseline ICS dose (medium or high dose). Two doses of study intervention will be administered in the clinic: the first at randomisation Visit 2 (Week 0) and the second at Visit 10 (Week 26). Participants will be assessed at each scheduled visit (a total of 17 study visits) during the 52-week treatment phase. Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 3, Visit 10, Visit 11, Exit Visit 17, and WS Visit (if applicable).

Participants who receive both doses of study intervention and complete the Exit Visit will be eligible to participate in an open-label extension (OLE) study (Study 212895), during which they will receive two doses of open-label GSK3511294 100 mg SC over another 52 weeks. Participants who do not enter the OLE study will have a follow-up visit/call at Week 56.

Independent Data Monitoring Committee: Yes

1.2. Schema



** R = Randomisation: To be randomised participants without a historical blood eosinophil count of ≥300 cells/µL must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. Participants will remain on their standard of care (SoC) asthma therapy throughout the intervention period and will be randomised 2:1 to receive GSK3511294 (100 mg) or placebo.*
*** SoC = medium to high dose ICS (≥440 µg FP HFA daily or clinical comparability) plus additional controller. SoC asthma therapy to exclude biologics.*
**** OLE = Open label extension. Willing participants will continue directly into OLE Study 212895. Participants unwilling to continue will have a follow-up visit 4 weeks after the Exit Visit.*

1.3. Schedule of Activities (SoA)

Protocol Activity	Pre-Screening	Screening/Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
General Eligibility Assessments																					
Informed consent [a]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote a.
Genetic sample informed consent [d]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote d.
Demography data collection	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; All females must be assessed at Visit 1 to determine childbearing potential.
Inclusion/Exclusion criteria	X	X																			
Historical blood eosinophil count		X																			See footnote e.
Medical history		X																			Include cardiovascular (CV), CV risk factors, asthma, exacerbations, vasculitis, allergies and anaphylaxis.
Smoking status		X																			
Parasite screening		X															X				Only required in regions with high-risk or for participants who have visited a high-risk region in the past 6 months. Use local laboratories for this test. For details refer to study reference manual (SRM).
eDiary registration and training		X																			Conduct thorough eDiary training at Screening Visit 1 and throughout the study on as-needed basis.

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Randomisation criteria			X																		Assess prior to randomisation; see footnote e.
Efficacy Assessments																					
Review for exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Collection of exacerbations at Visit 1 is historical data.
Spirometry (pre- and post-bronchodilator FEV_1)[h]		X	X								X							X	X		FEV_1=Forced expiratory volume in 1 second; Spirometry should not be conducted for participants with confirmed/suspected COVID-19 (see Section 8.2.3).
ACQ-5			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		ACQ-5=Asthma Control Questionnaire-5
Review eDiary (asthma symptoms, PEF summary)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PEF=Peak expiratory flow
HRQoL: PRO and Health Outcomes Assessments																					
SGRQ			X		X		X				X				X			X	X		SGRQ=St. George's Respiratory Questionnaire
PROMIS (fatigue items)			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PROMIS= Patient-reported outcomes measurement information system
SNOT-22			X								X							X	X		SNOT-22=Sino-nasal Outcomes Test-22 Questionnaire
Complete ADSD/ANSD		←========= daily =========→							X	X	X	X	X	X	X	X	X	X			ADSD/ANSD=Asthma Daily/Nightly Symptom Diary; To be completed daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Clinician-rated response to therapy							X				X				X			X	X		
Patient-rated response to therapy							X				X				X			X	X		
PGI-S		X	X				X		X		X				X			X	X		PGI-S: Patient Global Impression of Severity (of asthma)
PGI-C							X		X		X				X			X	X		PGI-C: Patient Global Impression of Change (from baseline of asthma severity)
Safety Assessments																					
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Ensure maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications are reviewed.
Physical Examination		X																X	X		Include height and weight for the complete physical exam at Screening Visit 1. Height can be omitted for subsequent visits.
Vital Signs		X	X			X			X		X	X			X		X	X	X		
12-lead ECG		X	X	X							X	X						X	X		ECG must be performed and assessed pre-dose. Twelve-lead ECG central over-read values should be used at all visits with the exception of Visit 2 and Visit 10 where 12-lead ECG machine read values should be used.

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
AE/SAE Assessment	X [g]	X [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE=Adverse events; SAE=Serious adverse events; see footnote g.
Laboratory Assessments																					
Haematology with white blood cell count [f]		X [e]	X	X	X	X	X		X		X	X	X		X		X	X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing; see footnotes e and f.
Total IgE			X																		
Clinical Chemistry		X	X		X	X	X		X		X	X			X		X	X	X		Include liver chemistry.
Pregnancy Test (WOCBP only)		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	Serum pregnancy test should be done at screening Visit 1 and Exit Visit/Withdraw from study visit; urine pregnancy tests should be done for all other assessments; WOCBP=Women of childbearing potential; See Section 8.3.5 for additional information.
Urinalysis		X	(X)								X							X	X		Conduct at Visit 2 if not completed at Visit 1. Note: dipstick, send for analysis if abnormality is identified by dipstick.
Anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			X																		ANA=antinuclear antibodies; MPO=myeloperoxidase; PR3=proteinase 3. Collected baseline sample will be stored and may be tested if necessary (see Section 7.5).
Complement C3 and C4			X				X				X				X			X	X		
PK sample			X	X	X	X	X		X		X	X	X		X			X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing.

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Immunogenicity sample			X	X	X	X	X				X	X	X	X	X			X	X		
Blood biomarker sample			X				X				X				X			X			Sample will be stored and may be analysed for exploratory biomarkers (see Section 8.7.3)
Genetics sample			←========== The genetics sample can be collected at Visit 2 or any visit after ==========→																		See footnote d.
Study intervention																					
Administer study intervention			X								X										Study intervention will only be administered in the clinic. Any scheduled assessments or sample draws should be performed beforehand. Monitor participant for at least 2h after administration (see Section 6.5).
eCRF/worksheets/other																					
Dispense Rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Register Visit in the IRT system		X	X								X								X		IRT=interactive response technology
Provide worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				The worksheet is a medical problems and healthcare utilisation worksheet.
Review worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
eDiary close out																		X	X		
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		eCRF=electronic Case Report Form

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	

a. Informed Consent must be obtained prior to initiating any study assessments. Pre-screening Visit 0 can occur any time from 0 to 14 days before Screening Visit 1.
b. Randomisation Visit 2 is 1 week after Screening Visit 1 but can be extended to up to 6 weeks after Visit 1 if, for example, a participant has an exacerbation during the run-in period. Results from Screening Visit 1 procedures must be available for review of randomisation criteria.
c. If a participant withdraws from the study, then the Withdraw from Study (WS) Visit should be conducted 26 weeks after the last administered dose of study intervention, i.e., at Week 26 if the second dose of study intervention was not received, or at Week 52 if the second dose of study intervention was received. A follow-up visit/call should also be conducted 30 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing.
d. Informed Consent for optional genetics research must be obtained before collecting a sample.
e. To be randomised, participants without a historical blood eosinophil count of ≥300 cells/µL in the 12 months prior to Screening Visit 1, must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. If the Screening Visit test result does not meet the blood eosinophil count eligibility criteria, the laboratory assessment may be repeated, at the discretion of the investigator, if it is judged to be likely in the eligible range for study inclusion within the run-in period prior to Visit 2.
f. For haematology samples collected after Randomisation, the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will not be reported to site staff and Sponsor (to maintain the treatment blind). However, sites will be sent total white blood counts throughout the study. Samples should be taken prior to dosing at Week 0 and Week 26 visits.
g. SAEs must be collected from signing of Informed Consent if considered related to study procedures.
h. If a patient fails the protocol-specified reversibility criterion or FEV_1 inclusion criteria, spirometry retest is allowed during the run-in period.

2. INTRODUCTION

2.1. Study Rationale

Anti-IL-5 therapies have an established efficacy and long-term safety profile and are a cornerstone of severe asthma management for patients with an eosinophilic phenotype [GINA, 2020]. Three antagonists of IL-5 (mepolizumab and reslizumab) or its receptor (IL-5R) (benralizumab) are approved for severe asthma with an eosinophilic phenotype, as an add-on treatment administered every 4 to 8 weeks.

GSK3511294 (depemokimab) is being developed as a LA SC injectable anti-IL-5 therapy and is anticipated to deliver an efficacy and safety profile similar to current anti-IL-5 therapies with a reduced dosing frequency (once every 26 weeks). The aim of this study is to investigate the efficacy and safety, over a 52-week treatment period, of GSK3511294 100 mg SC given once every 26 weeks as adjunctive therapy to participants with uncontrolled severe asthma with an eosinophilic phenotype.

2.2. Background

Persistent eosinophil inflammation is a feature of more than 50% of patients with severe asthma [Chung, 2014]. Several monoclonal antibodies (mAbs) targeting eosinophil inflammation have received marketing authorisation for asthma with an eosinophilic phenotype, including 3 targeting either interleukin-5 (IL-5) or its receptor (IL-5R): mepolizumab (Nucala™), reslizumab (Cinqair/Cinqaero), and benralizumab (Fasenra). All three, by utilising blood eosinophils as a biomarker to predict patients likely to respond to therapy, have been shown to reduce asthma exacerbations, and improve lung function and health-related quality of life (HRQoL), in patients with asthma with an eosinophilic phenotype [Haldar, 2009; Castro, 2011; Pavord, 2012; Bel, 2014; Ortega, 2014; Castro, 2015; Bleecker, 2016; FitzGerald, 2016; Chupp, 2017].

Evidence supporting the tolerability of targeting IL-5/5R is provided by long-term extension studies for mepolizumab [Lugogo, 2016; Khatri, 2019; Khurana, 2019], reslizumab [Murphy, 2017], and benralizumab [Busse, 2019] as well as efficacy data in real-world evidence settings for mepolizumab [Harrison, 2020; Bagnasco, 2019; Pertzov, 2019; Schleich, 2020]. Clinical trial data over more than 10 years combined with real-world evidence, have demonstrated that treatments targeting the IL-5 pathway are both highly effective and well-tolerated. Based on this established efficacy and safety, anti-IL-5/5R therapies are now a cornerstone of severe asthma management and are endorsed by international guidelines for appropriate patients that continue to exacerbate despite optimised care with Step 4 or Step 5 treatment (medium and high dose ICS) [GINA, 2020].

GSK3511294 is a humanised, affinity matured mAb that blocks human IL-5 binding to its receptor and belongs to the established class of anti-IL-5 therapies for severe asthma management. Compared with mepolizumab, GSK3511294 contains 7 amino acid substitutions to the heavy chain sequence: 4 amino acid changes introduced in the heavy chain variable region and 3 amino acid changes (YTE) in the Fc region. The resulting antibody has increased affinity and half-life. Evidence to date indicate that these amino

acid changes extend the pharmacokinetics (PK) and pharmacology of GSK3511294 to enable less frequent dosing with an anticipated similar efficacy and safety profile relative to mepolizumab (administered chronically).

Long-acting alternatives that can be administered on a less frequent basis are recognised as successful approaches for chronic indications. As a LA anti-IL-5 therapy, GSK3511294 is anticipated to have an efficacy and safety profile that is similar to those of the currently-approved therapies in its class, but with a single administration every 26 weeks, as opposed to the current regimen of every 4 weeks for mepolizumab and reslizumab, or every 8 weeks for benralizumab (every 4 weeks for the first 3 doses).

A detailed description of the chemistry, pharmacology, and safety of GSK3511294 is provided in the current Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2016N295843_03 or later].

2.3. Benefit: Risk Assessment

Summaries of findings from non-clinical studies conducted with GSK3511294 and completed FTIH study 205722 can be found in the current IB [GlaxoSmithKline Document Number 2016N295843_03 or later]. The following section outlines the risk assessment and mitigation strategy for this protocol:

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention GSK3511294		
• Allergic reactions including anaphylaxis.	• Allergic reactions with the most severe form being anaphylaxis (see Appendix 8), are potential risks associated with mAbs. • No allergic reactions or anaphylaxis have been reported with GSK3511294 in FTIH study 205722 in participants with mild to moderate asthma. One participant reported an event under Hypersensitivity SMQ with preferred term of rash verbatim "localised rash both bends of arms", 82 days post 30 mg SC dose of GSK3511294. The event was non-serious, of mild intensity, resolved within 10 days and was considered unrelated to the study intervention by the investigator.	• Daily monitoring of serious adverse events (SAEs) by Medical Monitor/SAE coordinator; regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GSK safety review team. • Use of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 8). • Participants will be monitored in clinic for immediate hypersensitivity and any other untoward effects for a minimum of 2 hours post-injection (both at randomisation and at Week 26). In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study intervention, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care if appropriate. • An independent data monitoring committee (IDMC) will review unblinded safety data at regular intervals.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Participants with severe allergic reaction/anaphylaxis with no alternative explanation after the first dose will not receive another dose.
• Type III Hypersensitivity (Immune complex disease/vasculitis)	• Adverse effects of vascular inflammation consistent with immune complex disease were observed in 1 female monkey in the 1-month toxicity study after administration of 10 mg/kg. A further monkey had a minimal focal inflammation after administration of 100 mg/kg. Immune complex disease was not observed in the 6-month repeat dose (2 doses) study at the same doses. It is unknown if this will translate to humans as preclinical models are not necessarily predictive of clinical findings in humans. • No AEs of Type III hypersensitivity have been reported with GSK3511294 in FTIH study 205722 in participants with mild to moderate asthma (36 participants received GSK3511294; 12 participants received placebo).	• Participants with current diagnosis of vasculitis will be excluded. Participants with high clinical suspicion of vasculitis at screening will be evaluated and excluded from enrolment if diagnosed (Section 5.2). • Daily monitoring of SAEs will be done by Medical Monitor/SAE coordinator; regular systematic review of adverse event (AE)/SAE data from ongoing studies will be performed by a GSK safety review team. • IDMC will review unblinded safety data at regular intervals; any events suggestive of immune complex disease will be reviewed by a rheumatologist (member of the IDMC). • Protocol guidance on early identification of vasculitis events is provided (see Section 7.5). • Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation after the first dose will not receive another dose of study intervention (see Section 7.1).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• Immunogenicity, anti-drug antibodies (ADAs)	• Biopharmaceutical products may elicit ADAs and neutralising antibodies (NAb), which have the potential to modulate PK or pharmacodynamics (PD), or to produce adverse reactions. • In FTIH study 205722, none of the participants tested positive for ADA at baseline. Overall, 9 participants (25%) had confirmed positive results for ADA at any time post-baseline, primarily in the GSK3511294 30 mg dose group (5 participants), which was also the group with the highest total serum IL-5 concentrations. This apparent correlation warrants further investigation. There were no major differences observed in the GSK3511294 plasma concentration profiles and blood eosinophil count-time profiles, as well as AE reporting between ADA-positive and ADA-negative participants. Neutralising antibodies were not tested in this study.	• Blood samples will be collected for detection of both ADA and NAb (see Section 8.8).
• Local injection site reactions	• A potential risk of any drug delivered via injection. • No injection site reactions were noted in the preclinical studies. • In the GSK3511294 FTIH study 205722, injection site reactions were reported by one (3%) participant who received GSK3511294 and one (8%) participant who received placebo.	• Daily monitoring of SAEs by Medical Monitor/SAE coordinator; regular systematic review of AE/SAE data from ongoing studies by GSK study team and/or GSK safety review team. • The IDMC will review unblinded safety data at regular intervals.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• QTc prolongation	• Four monkeys in the 6-month repeat dose monkey study administered 100 mg/kg every 3 months (2 doses) were observed to have QTc prolongation (mean change of 18 msec relative to vehicle control value) during Week 14. • In the GSK3511294 FTIH study (205722), no treatment effect for ECG parameters including corrected QT interval (QTcF) was observed across the GSK3511294 treatment groups (n=36). No participants met QTcF protocol specified criteria (QTcF >500 msec or increase from baseline >60 msec, or uncorrected QT >600 msec) that would require additional monitoring. • Analysis of the relationship between GSK3511294 plasma concentrations and change from baseline QTcF data collected in FTIH 205722 study did not reveal any clinically or statistically significant trends of concern with increasing GSK3511294 dose up to 300 mg. The predicted increase in mean QTcF change from baseline with GSK3511294 plasma concentrations point estimates remained below 10 msec [FDA, 2005] up to concentrations of 100 ug/mL, with a 95% lower CI consistent with zero change from baseline (i.e. the 95% lower bound of the CI is below zero) [GSK Document Number: 2020N457410_00].	• ECGs will be performed according to timepoints specified in the SoA (Section 1.3) and the assessment will be done as specified in Section 8.3.3. • Participants with QTc prolongation on screening will be excluded (criterion 15, Section 5.2). • Participants with a pre-existing clinically significant cardiac medical condition are excluded (criterion 7, Section 5.2). • Participants who meet QT stopping criteria as specified in Section 7.1.2 will not receive another dose of study intervention. • The IDMC will review unblinded safety data at regular intervals.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
• Risk of GSK3511294 affecting an unborn baby.	• Reproductive studies have not been conducted with GSK3511294; however, in the 6-month repeat dose monkey study no changes were observed in reproductive organs. Seminiferous tubules were evaluated with respect to their stage in the spermatogenic cycle and the integrity of the various cell types present within the different stages in sexually mature males. No cell or stage specific abnormalities were noted. • In addition, there is a low reproductive risk associated with the IL-5 target mechanism (as shown in pre-clinical reproductive toxicology studies of mepolizumab and reslizumab), a low genotoxic concern for mAbs in general, and a low transfer of mAbs into semen due to the inability of large molecular weight proteins such as GSK3511294 to access pivotal cells in the testes [Setchell, 1975; Pollanen, 1995; Pollanen, 1989; Setchell, 2001; Sohn, 2016], the risk of adverse effects on spermatogenesis is considered minimal. Therefore, male participants are not required to use contraception.	• Participants who are pregnant, breastfeeding, or plan to become pregnant at Screening are excluded (criterion 19, Section 5.2). Participants who become pregnant during the study will not receive another dose of study intervention (see Section 7.1). • All female participants will be assessed at screening to determine childbearing status. Female participants of childbearing potential must be using a highly effective contraceptive method from at least 14 days prior to first dose and until 30 weeks after the last administered dose as described in Section 10.4.2.
Study Procedures		
• Potential risk for injury with phlebotomy.	• Risks with phlebotomy include bruising, bleeding, infection, nerve damage.	• Procedures to be performed by trained personnel (i.e., study nurse).

2.3.2. Benefit Assessment

Current clinical data from approved anti-IL-5/5R mAbs (mepolizumab, reslizumab, and benralizumab) demonstrate clinical utility in the treatment of conditions associated with elevated eosinophil levels, such as severe asthma with an eosinophilic phenotype. Mepolizumab 100 mg SC (every 4 weeks) is approved as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype. The safety profile of mepolizumab is favourable.

As a LA anti-IL-5 mAb, GSK3511294 is anticipated to provide the same clinical benefit with a similar safety profile compared with mepolizumab and others in its class and with the added benefit of an extended duration of action requiring less frequent SC dosing (once every 6 months). As such, GSK3511294 may offer the convenience of an improved dosing schedule.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures being implemented to minimise risk to participants in this study, the potential risks of participating in this study are justified by the anticipated benefits that may be afforded to participants with severe uncontrolled asthma with an eosinophilic phenotype; therefore, the Sponsor considers that the investigation of the efficacy, and safety of GSK3511294 is justified in this study with a positive benefit: risk ratio.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks
Other	
• To investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	• Time to first clinically significant exacerbation[a] • Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit • Change from baseline in SGRQ total score at discrete timepoints during the 52-week period • Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period • SGRQ total score responder status at Week 52 (responder defined as achieving ≥4-point reduction from baseline) • ACQ-5 score responder status at Week 52 (responder defined as achieving ≥0.5-point reduction from baseline) • Change from baseline in Patient-Reported Outcomes Measurement Information Systems (PROMIS) Fatigue items score at

Objectives	Endpoints
	discrete timepoints during the 52-week period • Change from baseline in Asthma Daily Symptom Diary (ADSD)/ Asthma Nightly Symptom Diary (ANSD) weekly mean score at specified timepoints during the 52-week period • Change from baseline in awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean • Change from baseline in morning peak expiratory flow (PEF) 2-week mean • Change from baseline in daily asthma symptom scores 2-week mean • Change from baseline in mean number of occasions of rescue medication use/day 2-week mean • Mean number of days with oral corticosteroids (OCS) usage over 52 weeks • Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period • Change from baseline in Sino-nasal Outcomes Test-22 (SNOT-22) score at discrete timepoints during the 52-week period
• To investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient- and clinician-rated response to therapy • patient global impression of asthma severity and its change from baseline	• Patient-rated response to therapy at discrete timepoints during the 52-week period • Clinician-rated response to therapy at discrete timepoints during the 52-week period • Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period • Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during the 52-week period
• To investigate the PD effects of GSK3511294	• Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period

Objectives	Endpoints
• To investigate the PK of GSK3511294	• GSK3511294 plasma concentration at discrete timepoints during the 52-week period
Safety	
• To evaluate the safety and tolerability of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Incidence of AEs/SAEs • Laboratory parameters, including haematological and clinical chemistry parameters • Vital signs including blood pressure (BP), body temperature, and pulse rate • ECG assessments • Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294
Health Resource Use	
• To further evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on healthcare utilisation on top of existing asthma therapy	• Healthcare utilisation for asthma including hospitalisation, ED, and physician office/clinic visits

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

3.1. Primary Estimand

Population: Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Treatment comparison: GSK3511294 + SoC compared with placebo + SoC

Endpoint: Annualised rate of clinically significant exacerbations over 52 weeks

Main intercurrent events anticipated:

- Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e. regardless of the intercurrent event occurring
- Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be handled with a hypothetical strategy i.e. had the intercurrent event not occurred

- Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): to be handled with a treatment policy i.e. regardless of the intercurrent event occurring

Summary measure: Ratio of the rates of clinically significant exacerbations between GSK3511294 + SoC and placebo + SoC

For further details, see Section 9.4.

3.2. Secondary Estimands

Population: Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Treatment comparison: GSK3511294 + SoC compared with placebo + SoC

Endpoints:

- Change from baseline in SGRQ at Week 52
- Change from baseline in ACQ-5 at Week 52
- Change from baseline in pre-bronchodilator FEV_1 at Week 52
- Annualised rate of clinically significant exacerbations requiring hospitalisation and/or ED visit over 52 weeks

Main intercurrent events anticipated:

- Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e. regardless of the intercurrent event occurring
- Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be handled with a hypothetical strategy i.e. had the intercurrent event not occurred
- Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): to be handled with a treatment policy i.e. regardless of the intercurrent event occurring

Summary measures:

- Difference in mean change from baseline in SGRQ at Week 52
- Difference in mean change from baseline in ACQ-5 at Week 52
- Difference in mean change from baseline in pre-bronchodilator FEV_1 at Week 52
- Ratio of the rates of clinically significant exacerbations requiring hospitalisation and/or ED visit

between GSK3511294 + SoC and placebo + SoC.

For further details, see Section 9.4.

4. STUDY DESIGN

4.1. Overall Design

This study employs a multi-centre, randomised, placebo-controlled, double-blind, parallel group design. The study will recruit adults and adolescents (≥12 years) with a confirmed diagnosis of severe asthma with an eosinophilic phenotype and who are on a regimen of medium to high dose ICS (≥440 mcg fluticasone propionate [FP] hydrofluoroalkane product [HFA] daily, or clinically comparable [GINA, 2020; see Appendix 10]) plus at least one additional controller medication, with evidence of bronchodilator reversibility or airway hyperresponsiveness as measured by methacholine/histamine challenge. Eligible participants must have uncontrolled asthma with a history of repeat exacerbations (≥2 exacerbations in the previous 12 months) while on their existing maintenance asthma therapy that excludes any biologics. Participants will be required to have a blood eosinophil count of ≥150 cells/µL at screening or ≥300 cells/µL documented in the 12 months prior to screening. Participants who have received any anti-IL-5/5R mAb therapy within the last 12 months will be excluded from this study.

Participants will attend a Pre-screen Visit (Visit 0) to sign consent and a Screening Visit (Visit 1; may be done on the same day as Visit 0) for eligibility assessments (see Section 8.1). At the conclusion of the run-in period (Visit 2), participants who meet the pre-defined criteria (see Section 5.1 and Section 5.3) will be randomised in a 2:1 ratio to receive either GSK3511294 100 mg or placebo, administered SC (at Week 0 and Week 26) in the clinic via a pre-filled safety syringe (PFS) as an adjunct therapy. Randomisation will be stratified based on baseline ICS dose (aiming to up to 50% approximately of participants on medium ICS dose; see Appendix 10). Participants will remain on their existing stable maintenance asthma therapy throughout the study (See Section 6.9 for details on concomitant medications). See Section 4.1.1 for additional details on the study phases, duration, and treatment arms.

The primary outcome measure will be the annualised rate of clinically significant exacerbations (i.e. exacerbations requiring systemic CSs and/or hospitalisation and/or ED visit [see Section 8.2.2]) measured over the 52-week treatment period. Additional efficacy assessments will include lung function (pre- and post-bronchodilator FEV_1), asthma control (ACQ-5), HRQoL measured with SGRQ, fatigue (PROMIS items), nasal symptoms (SNOT-22 questionnaire), daytime and night-time asthma symptoms (ADSD/ANSD), and daily electronic diary (eDiary) parameters including peak flow, rescue use, daily symptoms and nocturnal awakening due to asthma (see Section 8.2).

The study will include safety (see Section 8.3 and Section 8.4) and immunogenicity (see Section 8.8) assessments to characterise the safety profile of GSK3511294 100 mg SC following repeat dosing. In addition, blood samples will be collected for assessment of PD effects (blood eosinophils) (see Section 8.7) and PK of GSK3511294 (see Section 8.5).

After randomisation, all participants will be encouraged to remain in the study and complete all scheduled visits, regardless of whether they receive the second dose of study intervention at Week 26. Participants who experience any of the study intervention

discontinuation conditions (listed in Section 7.1) will not receive another dose of study intervention.

Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 3, Visit 10, Visit 11, Exit Visit 17, and WS Visit (if applicable). Participants who are unable to attend their scheduled clinic visits due to COVID-19 restrictions or other unexpected events may complete some visits at home (see Appendix 11). Note: study intervention will only be administered in the clinic (at Week 0 and Week 26 visits).

4.1.1. Study Phases, Duration and Treatment Arms

At pre-screening, participants will be requested to participate in the study for a maximum of 60 weeks (Visit 0 to the Exit Visit, inclusive) or 64 weeks if not continuing into the OLE Study 212895 (Visit 0 to the Follow-up Visit, inclusive).

During the study, participants will remain on their existing maintenance asthma therapy whilst completing all phases of the study described in Table 1.

Table 1 Study Phases

Phase	Phase Title	Duration	Description
1	Pre-screening (Visit 0)	0-2 weeks	Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) but must be completed prior to initiating any Visit 1 procedures
2	Screening (Visit 1) and Run-in	1-6 weeks	Participants who meet all the eligibility criteria at Screening (Visit 1) will enter the run-in period for a minimum of 1 week and a maximum of 6 weeks. The run-in is intended to assess the participant's compliance with study-related procedures and continued eligibility for the study as well as to collect baseline eDiary data. Participants who experience an asthma exacerbation during the run-in period should receive treatment for their exacerbation and remain in the run-in period until the investigator considers that the participant has returned to their baseline asthma status for at least one week. The participants that are not eligible to continue in the study at the end of the run-in period will be deemed run-in failures, but may be rescreened after consultation with the Medical Monitor (Section 5.5).

Phase	Phase Title	Duration	Description
3	Study Intervention (Visit 2-Visit 17)	52 weeks	Participants who meet the randomisation criteria will enter the 52-week treatment period and will be randomised to receive either add-on **GSK3511294 (100 mg) or matching placebo in a 2:1 ratio.** During the treatment phase, a total of 2 doses of study medication will be administered SC via PFS: at Week 0 (Visit 2) and Week 26 (Visit 10).[a] Study visits will occur at Week 0, Week 2, Week 4 and every 4 weeks thereafter with an additional study visit at Week 26 for the administration of the second dose of study intervention. The study intervention period will conclude with the Exit Visit at Week 52 (Visit 17).
Only participants who choose not to enter the OLE study will complete the phase below:			
4	Follow-up	4 weeks	Participants will complete a Follow-up visit/call 4 weeks after the Exit Visit; this visit/call will capture AE/SAE assessments and a urine pregnancy test result. At the end of the Follow-up visit/call, participants will be prescribed appropriate alternative asthma therapy at the physician's discretion, if required.

a. Participants who experience any of the study intervention discontinuation conditions listed in Section 7.1 will not receive another dose of study intervention but will be encouraged to remain in the study and complete their remaining scheduled visits/assessments.

4.1.2. Treatment after the End of Study

Participants who receive both doses of double-blind treatment and complete the Week 52 Exit Visit will be eligible to participate in the OLE study 212895. See Section 6.7 for details.

Participants who are not entering the OLE study 212895 will enter a 4-week follow-up period and complete the study with a Follow-up visit/call at Week 56. After study completion, appropriate alternative asthma therapy may be prescribed at the physician's discretion.

4.1.3. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilised in this study to ensure external objective review of the data in order to protect the ethical and safety interests of participants and to protect the scientific validity of the study (see Section 10.1.5).

4.2. Scientific Rationale for Study Design

Population: This study is designed to evaluate the efficacy and safety of GSK3511294 100 mg SC as an adjunct therapy in participants with severe uncontrolled asthma with an eosinophilic phenotype. Participants should have uncontrolled asthma, as evidenced by repeat exacerbations, despite treatment with optimised background therapy consisting of maintenance ICS treatment and at least one additional controller. Participants are also required to have the requisite elevated blood eosinophil count (see randomisation criterion 1, Section 5.3) that is indicative of asthma with an eosinophilic phenotype. This population has been shown to benefit from add-on anti-IL-5 therapies such as mepolizumab [Pavord, 2012, Ortega, 2014; Chupp, 2017] and is therefore anticipated to benefit from GSK3511294.

Blood eosinophil count screening: A Screening blood eosinophil count threshold of ≥150 cells/µL at Screening Visit 1 or ≥300 cells/µL in the previous 12 months has been selected as a criterion to identify participants likely to respond to treatment with anti-IL-5 therapy, consistent with findings from previous trials with mepolizumab.

Primary efficacy endpoint: A primary efficacy endpoint of annualised rate of clinically significant exacerbations has been selected as a robust and clinically relevant measure of the direct benefit of GSK3511294 to a population with severe uncontrolled asthma with an eosinophilic phenotype. In the current study, the definition of clinically significant exacerbations (see Section 8.2.2), i.e. exacerbations treated with systemic CSs (intramuscular [IM], intravenous [IV], or oral) for 3 or more days and/or hospitalisation and/or ED visit, is consistent with previous trials with mepolizumab [Pavord, 2012; Ortega, 2014] and reslizumab [Castro, 2015].

Placebo-control design: An established randomised, double-blind and parallel-group study design will allow for a robust determination of participant response to GSK3511294 as an adjunct therapy to their maintenance asthma therapy. As such, the comparator arm in this study will be placebo plus continued maintenance asthma treatment. A 2:1 randomisation will be used in order to limit the number of participants randomised to placebo treatment and to provide more safety information on GSK3511294. All participants will continue to receive their optimised and stable maintenance asthma therapy throughout the entire duration of the study regardless of intervention arm assignment. The stable maintenance asthma therapy (per the inclusion criteria) will consist of medium to high dose ICS (≥440 mcg FP HFA daily, or clinically comparable [GINA, 2020; see Appendix 10]) with at least one additional controller medication e.g., long-acting beta-2-agonist (LABA), with or without maintenance oral corticosteroids (OCS). Participants who are treated with medium dose ICS will also need to be treated with LABA to qualify for inclusion.

Study Duration: A 52-week treatment period should allow sufficient time to assess whether GSK3511294 100 mg SC, administered as two repeat doses 26 weeks apart (at Week 0 [randomisation] and at Week 26), can reduce the annualised rate of clinically significant exacerbations to a similar extent to that observed with other anti-IL-5 mAbs. The study will also provide 12-month safety data with repeat dosing.

Run-in Period: The one-week (maximum 6 weeks) Run-in period allows for the assessment of participant understanding and compliance with the daily eDiary, to establish Baseline symptoms, and to allow adequate time for receipt of results from assessments collected at Screening Visit 1.

Open-label extension study: Following study completion, all eligible participants will have the option to participate in the OLE study to provide additional safety data (see Section 6.7).

Data collection after discontinuation from study intervention: The protocol objective is to collect data over the full study period, whether participants continue on study intervention or in the case of premature discontinuation from study intervention. However, the decision to continue in the study after premature discontinuation from study intervention remains the prerogative of the participant. Participants who agree to continue in the study after premature discontinuation from study intervention (for any reason) will continue to be contacted by the study site, either through in clinic visits or by phone as agreed with the participant, on a monthly basis (aligned to their study schedule) until the end of their planned 52-week participation and follow up contact 4 weeks later, to enable capture of post-intervention information.

4.2.1. Participant Input into Design

Participant involvement in the study design was obtained from 10 patients (6 in Italy, 1 in UK, and 3 in US [1 adolescent]) using 2 online qualitative surveys containing 17 questions over a period of 2 weeks. Based on the participant feedback, the following design elements will be implemented:

- Reduced number of laboratory samples and patient-reported outcomes (PRO) assessments
- A hybrid trial model, allowing for home visits and virtual/telemedicine visits at key assessments which will reduce the burden of onsite visits and offer some flexibility in visit timing for the participant's schedule

4.3. Justification for Dose

The dose rationale for this study is supported by the FTIH Study 205722 [GlaxoSmithKline Document Number 2019N411063_00] that investigated single SC doses of GSK3511294 ranging from 2 mg to 300 mg. The FTIH study was designed to collect robust blood eosinophil pharmacology data (including washout) in a relevant population (mild to moderate asthma and a blood eosinophil count ≥200 cells/µL at screening) and inform dose selection in late-phase development using Model-informed drug development (MIDD) principles [Wang, 2019; Marshall, 2019]. The precedence of using blood eosinophil reduction as a predictor of efficacy in severe asthma with an eosinophilic phenotype was established in two mepolizumab Phase 3 studies, which consistently reduced annualised exacerbation rate by approximately 50%, for associated reductions in blood eosinophils of 84% in the MENSA trial [Ortega, 2014] and 78% in the MUSCA trial [Chupp, 2017], compared with placebo. Since GSK3511294 targets the same IL-5 epitope as mepolizumab, establishing the same reduction in blood eosinophils

as mepolizumab via the same IL-5 neutralisation is expected to generate the same clinical efficacy in the same patient population (i.e., severe asthma with an eosinophilic phenotype with a previous history of two or more exacerbations in the past 12 months). In addition, given the precedented safety profile of IL-5 neutralisation comparable to placebo, targeting previous mepolizumab pharmacology is both valid and expeditious in selecting the dose of GSK3511294.

A comprehensive analysis of the clinical effects of GSK3511294 on blood eosinophils from Study 205722 was therefore conducted to identify the dose and frequency of dosing that match previous Phase 3 mepolizumab target pharmacology most closely. To this end, a Bayesian non-linear mixed-effects dose-time response model was used to analyse blood eosinophil data. This model was then used to calculate the posterior probability of achieving reductions of 78% for the MUSCA trial [Chupp, 2017] and 84% for the MENSA trial [Ortega, 2014] compared with placebo. Doses deemed suitable were defined as having a probability of exceeding MUSCA in excess of 80% while doses deemed unsuitable as having a probability of exceeding MENSA of less than 10%.

Based on the comprehensive analysis of the clinical effects of GSK3511294 on blood eosinophils, a dose of 100 mg SC GSK3511294 administered every 26 weeks has been selected to match the pharmacology seen with mepolizumab in two Phase 3 studies at the approved therapeutic dose, but over an extended period of 26 weeks [GSK Document Number 2019N418119_00].

4.4. End of Study and Study Completer Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed the visit at Week 52, regardless of whether the second dose of study intervention (at Week 26) was received.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if **all** of the following criteria apply:

AGE

1. **Age:** Adults and adolescents ≥12 years of age, at the time of signing the informed consent/assent.

   [For countries where local regulations or the regulatory status of study medication permit enrolment of adults only, participants recruited will be ≥18 years of age]

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS

2. **Asthma:** Participants must have a documented physician diagnosis of asthma for ≥2 years that meets the National Heart, Lung, and Blood Institute guidelines [NHLBI, 2007] or GINA guidelines [GINA, 2020] **AND**

   a) **Eosinophilic phenotype:** Have, or with high likelihood of having, asthma with an eosinophilic phenotype as per Randomisation Criteria 1 and 2 (see Section 5.3)

   AND

   b) **Exacerbation history:** Have previously confirmed history of ≥2 exacerbations requiring treatment with systemic CS (IM, IV, or oral), in the 12 months prior to Visit 1, despite the use of medium to high-dose ICS (see criterion 4). For participants receiving maintenance CS, the CS treatment for the exacerbations must have been a two-fold dose increase or greater.

3. **Airflow obstruction:** Persistent airflow obstruction as indicated by:

   a) For participants ≥18 years of age at Visit 1, a pre-bronchodilator FEV_1 <80% predicted (NHANES III) recorded at Visit 1

   b) For participants 12-17 years of age at Visit 1:

   - A pre-bronchodilator FEV_1 <90% predicted (NHANES III) recorded at Visit 1 **OR**
   - FEV_1:Forced Vital Capacity (FVC) ratio <0.8 recorded at Visit 1

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4. **Inhaled Corticosteroid:** A well-documented requirement for regular treatment with medium to high dose ICS (in the 12 months prior to Visit 1 with or without maintenance OCS). The maintenance ICS dose must be ≥440 mcg FP HFA daily, or clinically comparable [GINA, 2020; see Appendix 10]. Participants who are

treated with medium dose ICS will also need to be treated with LABA to qualify for inclusion.

5. **Additional Controller Medication:** Current treatment with at least one additional controller medication, besides ICS, for at least 3 months [e.g., LABA, long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonist (LTRA), or theophylline].

SEX

6. **Male or eligible female.**

   Female Participants:

   - A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
     - Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4.1

       OR

     - Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4.2 from at least 14 days prior to the first dose of study intervention until at least 30 weeks after the last administered dose of study intervention.
   - A WOCBP must have a negative highly sensitive serum pregnancy test at screening Visit 1 and a negative highly sensitive urine pregnancy test within 24 hours before the first dose of study intervention. Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.
   - Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
   - The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated in relationship to the first dose of study intervention).
   - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

     Note: If the childbearing potential changes after start of the study (e.g., a premenarcheal female participant experiences menarche) or the risk of pregnancy changes (e.g., a female participant who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine if a female participant must begin a highly effective method of contraception. If reproductive status is questionable, additional evaluation should be considered.

INFORMED CONSENT
7. **Informed Consent:** Capable of giving signed informed consent/assent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. **French participants:** In France, a participant will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

MEDICAL CONDITIONS
1. **Concurrent Respiratory Disease:** Presence of a known pre-existing, clinically important lung condition other than asthma. This includes (but is not limited to) current infection, bronchiectasis, pulmonary fibrosis, bronchopulmonary aspergillosis, or diagnoses of emphysema or chronic bronchitis (chronic obstructive pulmonary disease other than asthma) or a history of lung cancer. 2. **Eosinophilic Diseases:** Participants with other conditions that could lead to elevated eosinophils such as hyper-eosinophilic syndromes including (but not limited to) Eosinophilic Granulomatosis with Polyangiitis (EGPA, formerly known as Churg-Strauss Syndrome) or Eosinophilic Esophagitis. 3. **Parasitic infection:** Participants with a known, pre-existing parasitic infestation within 6 months prior to Visit 1. 4. **Immunodeficiency:** A known immunodeficiency (e.g. human immunodeficiency virus – HIV), other than that explained by the use of CSs taken as therapy for asthma. 5. **Malignancy:** A current malignancy or previous history of cancer in remission for less than 12 months prior to screening (Participants that had localised carcinoma of the skin which was resected for cure will not be excluded). 6. **Liver Disease:** Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice. NOTE: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) are acceptable if participant otherwise meets entry criteria. 7. **Other Concurrent Medical Conditions:** Participants who have known, pre-existing, clinically significant cardiac, endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.

MEDICAL CONDITIONS

8. **Vasculitis:** Participants with current diagnosis of vasculitis. Participants with high clinical suspicion of vasculitis at screening will be evaluated and current vasculitis must be excluded prior to enrolment.
9. **COVID-19:** Participants that, according to the investigator's medical judgment, are likely to have active COVID-19 infection should be excluded. Participants with known COVID-19 positive contacts within the past 14 days should be excluded for at least 14 days following the exposure during which the participant should remain symptom-free.

PRIOR/CONCOMITANT THERAPY

10. **Monoclonal antibodies targeting IL-5/5R:** Participants who have received mepolizumab (Nucala™), reslizumab (Cinqair/Cinqaero), or benralizumab (Fasenra) within 12 months prior to Visit 1 or who have a previous documented failure with anti-IL-5/5R therapy.
11. **Other mAbs in the treatment of asthma**: Participants who have received omalizumab (Xolair) or dupilumab (Dupixent) within 130 days prior to Visit 1.
12. **Other mAbs not used for the treatment of asthma:** Participants who have received any mAb within 5 half-lives of Visit 1. Authorized treatments for COVID-19 are permitted.
13. **Investigational Medications:** Participants who have received treatment with an investigational drug within the past 30 days or five terminal phase half-lives of the drug whichever is longer, prior to Visit 1 (this also includes investigational formulations of marketed products).

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

14. **Previous participation:** Previously participated in any study with mepolizumab, reslizumab, or benralizumab and received study intervention (including placebo) within 12 months prior to Visit 1.

DIAGNOSTIC ASSESSMENTS

15. **ECG Assessment:** QTcF ≥450 msec or QTcF ≥480 msec for participants with Bundle Branch Block in the 12-lead ECG central over-read from screening Visit 1.

OTHER EXCLUSIONS

16. **Smoking history:** Current smokers or former smokers with a smoking history of ≥10 pack years (number of pack years = (number of cigarettes per day / 20) x

OTHER EXCLUSIONS

number of years smoked). A former smoker is defined as a participant who quit smoking at least 6 months prior to Visit 1.

17. **Alcohol/Substance Abuse:** A history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1.
18. **Hypersensitivity:** Participants with allergy/intolerance to the excipients of GSK3511294 in Section 6.1 or any mAb or biologic.
19. **Pregnancy:** Participants who are pregnant or breastfeeding. Participants should not be enrolled if they plan to become pregnant during the time of study participation. Requirements for pregnancy testing are located in Section 8.3.5.
20. **Adherence:** Participants who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations.

5.3. Randomisation Criteria

At the end of the run-in period, study participants must fulfil all of the randomisation inclusion/exclusion criteria below in order to be randomised to study intervention.

5.3.1. Randomisation Inclusion Criteria

RANDOMISATION INCLUSION CRITERIA

1. **Blood eosinophil count:**
   a) An elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past 12 months prior to Visit 1 that is related to asthma

      OR

   b) An elevated peripheral blood eosinophil count of ≥150 cells/μL at Screening Visit 1 that is related to asthma.
2. **Asthma:** Evidence of airway reversibility or responsiveness as documented by either:
   a) Airway reversibility (FEV_1≥12% and 200 ml) demonstrated at Visit 1 or Visit 2 using the Maximum Post Bronchodilator Procedure **OR**
   b) Airway reversibility (FEV_1≥12% and 200ml) documented in the 24 months prior to Visit 2 (randomisation visit) **OR**
   c) Airway hyperresponsiveness (methacholine: PC_{20} of <8 mg/mL, histamine: PD_{20} of <7.8 μmol, mannitol: decrease in FEV_1 as per the labelled product instructions) documented in the 24 months prior to Visit 2 (randomisation visit)
3. **eDiary compliance:** Compliance with completion of the eDiary defined as completion of all questions on 4 or more days out of the 7 days immediately preceding Visit 2.

5.3.2. Randomisation Exclusion Criteria

RANDOMISATION EXCLUSION CRITERIA

1. **Laboratory abnormality:** Evidence of clinically significant abnormality in the haematological, biochemical or urinalysis screen at Visit 1, as judged by the investigator.
2. **Liver chemistry test:** Participants who meet the following based on results from sample taken at Screening Visit 1:
   a) Alanine aminotransferase (ALT) >2x upper limit of normal (ULN)
   b) Total bilirubin >1.5x ULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
   c) Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice.

   NOTES: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) is acceptable if the participant otherwise meets entry criteria.
3. **ECG:** QTcF ≥450msec, or QTcF ≥480 msec for participants with Bundle Branch Block, in the 12-lead ECG machine read at randomisation Visit 2 are excluded. Participants are excluded if an abnormal ECG finding from central over-read of the 12-lead ECG conducted at Screening Visit 1 is considered to be clinically significant and would impact the participant's participation during the study, based on the evaluation of the Investigator.
4. **Unstable Asthma:** Participants with a clinically significant asthma exacerbation in the 7 days prior to randomisation should have their randomisation visit delayed until the investigator considers the participant's asthma to be stable (see Section 5.6).
5. **Maintenance Asthma Therapy:** Any changes in the dose or regimen of baseline ICS and/or additional controller medication (except for treatment of an exacerbation) during the run-in period.

5.4. Lifestyle Considerations

No lifestyle restrictions are required for this study.

5.5. Pre-screen/Screen/Run-in Failures

Pre-screen/screen/run-in failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information

includes demography, screen failure details, eligibility criteria, any protocol deviations and any SAEs.

For the purposes of this study, pre-screen/screen/run-in failures will be defined as follows:

Pre-screen Failures	Screen Failures	Run-in Failures
Participants who are assigned a study number at the time of signing the informed consent (pre-screen visit) but do not progress to the screening visit.	Participants who complete at least one additional Visit 1 (Screening) procedure but do not enter the run-in period.	Participants who enter the run-in period but are not subsequently randomised.

Re-screening of participants will be permitted; however, advance written approval to proceed with re-screening a participant must be obtained from the Medical Monitor.

Re-screened participants should be assigned a new participant number for every screening/rescreening event.

5.6. Criteria for Temporarily Delaying Randomisation

Participants who experience a clinically significant asthma exacerbation during the run-in period should receive treatment for their exacerbation, have their randomisation visit delayed and remain in the run-in period (up to 6 weeks) until the investigator considers the participant to have returned to their baseline asthma status for at least 7 days.

A clinically significant exacerbation is defined as worsening of asthma requiring the use of systemic CS and/or hospitalisation and/or ED visit (Section 8.2.2).

A participant who is not eligible to continue in the study at the end of the run-in period, should be considered a run-in failure but may be rescreened after consultation with the Medical Monitor (Section 5.5).

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s)/product(s) (IP), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Study intervention will only be administered in the clinic; hence Visit 2 (Week 0) and Visit 10 (Week 26) are required to be in-clinic visits.

6.1. Study Intervention Administered

GSK3511294 is a humanised IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. GSK3511294 liquid drug product will be supplied by GSK in a Type I glass syringe (with a 1/2-inch, 29-gauge thin wall, staked needle and sealed with a latex-free rubber plunger). The drug product and syringe will be assembled in a single use, disposable safety syringe to enable delivery of the drug product. Each device enables SC delivery of 100 mg GSK3511294 in 1.0 mL sterile liquid formulation. The formulation contains L-histidine, trehalose dihydrate, L-arginine hydrochloride, disodium edetate (EDTA), water for injection and polysorbate 80.

The placebo in this study will be 0.9% sodium chloride solution contained in a PFS also supplied by GSK.

An overview of study intervention is provided in Table 2.

Table 2 Overview of Study Intervention

ARM Name	GSK3511294 100 mg	Placebo
Intervention Name	GSK3511294 100 mg SC	Placebo
Type	Biologic	N/A
Dose Formulation	Sterile liquid formulation in single-use PFS	Sterile 0.9% (w/v) sodium chloride solution in single-use PFS
Unit Dose Strength(s)	100 mg/mL; 1.0 mL (deliverable)	N/A, 1.0 mL (deliverable)
Dosage Level(s)	100 mg once every 26 weeks (Week 0 and Week 26)	Placebo once every 26 weeks (Week 0 and Week 26)
Route of Administration	SC injection	SC injection
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.	Study Intervention will be provided in PFS. Each PFS will be labelled as required per country requirement.

PFS=Pre-filled safety syringe, IMP=Investigational Medicinal Product, N/A=not applicable

6.1.1. Medical Devices

The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are injection devices:

- A pre-filled syringe contained within a safety syringe. The devices used in the study are representative of the devices planned to be marketed for the product.
- The components that comprise the pre-filled syringe (glass barrel with pre-staked needle and plunger) are sourced from Becton Dickinson. The pre-filled syringe is filled with study intervention (GSK3511294 or placebo) and assembled at GSK, Barnard Castle.
- The safety syringe components are manufactured by Becton Dickinson. The safety syringe components are assembled with the pre-filled syringe at GSK, Barnard Castle.

The Instruction for use (IFU) of the injection device will be provided. The instructions were developed and optimised as a result of formative human factors studies for mepolizumab and are representative of those that are planned for GSK3511294.

All device deficiencies, (including malfunction, use error and inadequate labelling) shall be documented, and reported by the investigator throughout the clinical investigation (see Section 8.4.8) and appropriately managed by GSK.

6.2. Packaging and Labelling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.3. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention.
- All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the SRM.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.4. Measures to Minimise Bias: Randomisation and Blinding

6.4.1. Treatment Assignment

- Eligible participants will be centrally randomised using an IRT system.
- The randomisation schedule will be generated using the GSK validated randomisation software RandAll NG. Separate randomisation schedules will be created for each country. Participants will be assigned to study intervention in accordance with the randomisation schedule. Once a randomisation number has been assigned to a participant, it cannot be reassigned to any other participant in the study.
- Randomisation will be stratified according to the participant's baseline ICS dose (aiming to up to 50% approximately of participants on medium ICS dose; see Appendix 10).
- At Visit 2 (Week 0), those participants who meet the randomisation criteria will be randomised in a 2:1 ratio to receive one of the following study treatments in addition to their stable maintenance asthma treatment:
    - GSK3511294 100 mg SC
    - Placebo SC
- Study intervention will be administered in the clinic at Visit 2 (Week 0) and Visit 10 (Week 26) as per the SoA (Section 1.3).

6.4.2. Blinding

- The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded, GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.
- Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, GSK3511294 and placebo will be administered from PFSs that will be identical in appearance.
- If a participant's intervention code is unblinded by the investigator or treating physician, that participant will continue with all study visits but will not receive the

second dose of study intervention at Week 26. The primary reason for the event or condition which led to the unblinding will be recorded in the CRF (see Section 7.1).

- To maintain the blind, haematology data (absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes) from post-randomisation samples will not be reported to the site or the central study team.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4.3. Controlled Early Access to Unblinded PK and PKPD Data

Designated independent representative(s) may be unblinded for performing population PK and PKPD dataset preparation and draft PK and PKPD model development using scrambled (random reassignment of subject identification numbers) PK and PKPD unblinded datasets, including baseline demographic characteristics. No adverse event data or efficacy data will be included.

6.5. Study Intervention Compliance

Both doses of GSK3511294 or placebo will be administered under medical supervision via SC injection to participants by the investigator or designee at the study site. Dose administration details (date and time) will be recorded in the source documents and reported in the CRF.

Participants will be monitored in clinic for a minimum of 2 hours post-dose to monitor for immediate hypersensitivity and any other untoward effects. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of GSK3511294, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the participant to another facility for additional care if appropriate.

6.6. Dose Modification

Dose modification is not allowed.

6.7. Continued Access to Study Intervention after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition whether or not GSK is providing specific post-study treatment.

At the end of the study, participants will be eligible to screen to enter the OLE Study 212895 and have continued access to open-label GSK3511294 if he/she:

- has received both doses of study intervention (at Week 0 and Week 26), AND
- completed the scheduled Exit Visit at Week 52, AND
- did not meet any of the study intervention discontinuation conditions (Section 7.1) during the study.

For participants who enrol into the 12-month OLE study, the Day 1 visit of the OLE study can occur on the same day as the Exit Visit of the current study. Specific details on the OLE study will be documented separately.

Participants who do not enter the OLE study will complete a follow-up visit/call and be prescribed alternative asthma therapy if needed and as determined by the study investigator.

6.8. Treatment of Overdose

The dose of GSK3511294 that is considered to be an overdose has not been defined. There are no known antidotes and there is no specific treatment for a suspected overdose. In FTIH study 205722 (refer to the current IB [GlaxoSmithKline Document Number 2016N295843_03 or later]), single SC doses of GSK3511294 up to 300 mg were well tolerated by adult participants with mild/moderate asthma (6 participants received a 300 mg SC dose).

Each PFS will enable the delivery of a single dose of study intervention (see Section 6.1). In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Treat the participant with active supportive care as dictated by the participant's clinical status in the knowledge of the long half-life (approximately 41 days) of GSK3511294.
- Closely monitor the participant for AE/SAE and laboratory abnormalities for 30 weeks following the last administered dose.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding discontinuation or delay of another dose of study intervention will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.9. Concomitant Therapy

At pre-screening and/or screening, information on the participant's baseline maintenance asthma therapy will be collected and recorded in the eCRF.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded in the eCRF along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency (any dose changes are to be recorded for OCS)

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Permitted Medications and Non-Drug Therapies

Throughout the study, participants are to be maintained on their baseline maintenance asthma treatment consisting of ICS plus at least one other controller, e.g. LABA, LAMA, with or without maintenance OCS (see inclusion criteria 4 and 5, Section 5.1). It is recognised that in a year-long study, changes may need to be individualised if clinically crucial for a participant. The investigator is encouraged to discuss any cases with the Medical Monitor before initiating changes to a participant's maintenance asthma medication.

Additional asthma medications such as theophyllines and anti-leukotrienes will be permitted as maintenance provided that they have been taken regularly in the 3 months prior to screening (Visit 1). If uncertain whether a medication is permitted, please confirm with the Medical Monitor.

Albuterol/salbutamol is permitted throughout the study but should be withheld in the 6-hour period prior to spirometry assessments, if possible. Study-provided albuterol/salbutamol should not be recorded in the eCRF, only in the eDiary.

LABAs, LAMAs, and fixed dose combinations of ICS/LABA or ICS/LABA/LAMA should be withheld for ≥12 hours prior to spirometry, if possible.

Continuous Positive Airway Pressure (CPAP) or Bilevel Positive Airway Pressure (BiPAP) for the treatment of obstructive sleep apnoea is permitted, if initiated prior to the Screening Visit (Visit 1). This treatment must be captured in the eCRF.

Allergen-specific immunotherapy is permitted provided that it has been taken regularly in the 6 months prior to screening (Visit 1).

Participants can be vaccinated against SARS-CoV-2 infection using authorized COVID-19 vaccines in line with local/national guidelines for COVID-19 vaccines. Experimental COVID-19 vaccines are not permitted.

COVID-19 vaccine administration and the administration of the study intervention should be separated by 14 days if possible, in order to be able to properly assess study injection site/treatment reactions.

Participants can be treated for SARS-CoV-2 infection using authorized COVID-19 treatments (including monoclonal antibodies) in line with local/national guidelines. Experimental COVID-19 treatments are not permitted.

6.9.2. Prohibited Medications and Non-Drug Therapies

The following medications are not allowed prior to screening (Visit 1), according to the following schedule, or during the study:

Medication	**Washout Time Prior to Screening Visit**
Investigational drugs	1 month or 5 half-lives whichever is longer
Omalizumab [Xolair], dupilumab [Dupixent]	130 days
Mepolizumab [Nucala™], reslizumab [Cinqair/Cinqaero], benralizumab [Fasenra]	12 months
Other monoclonal antibodies	5 half-lives
Experimental anti-inflammatory drugs (non biologicals)	3 months

Immunosuppressive medications such as those listed below (not all inclusive)
Corticosteroids if used to treat a condition other than asthma • Intramuscular, long-acting depot • Regular systemic (oral or parenteral)
Methotrexate, cyclosporin, azathioprine
Oral gold
Chemotherapy used for conditions other than asthma

Additionally, Bronchial Thermoplasty and Radiotherapy are excluded for 12 months prior to Visit 1 and throughout the study. CPAP, BiPAP, and oxygen therapy should not be initiated during the run-in period.

6.9.3. Rescue Medicine

Trade label albuterol/salbutamol metered dose inhalers (MDIs) will be provided as rescue medication throughout the study. Albuterol/salbutamol will be sourced for all centres. Use of low dose ICS-formoterol as rescue medication is not allowed during the study.

Participants will be dispensed an MDI at Screening Visit 1 to be used primarily to treat asthma symptoms on an as needed basis and also during the reversibility assessments (see Section 8.2.3.1). The MDI should be replaced as needed.

Although the use of rescue medications is allowable (at any time during the study), the use of rescue medications should be withheld, if possible, for at least 6 hours prior to the spirometry assessments. Rescue medication usage will be recorded in the eDiary.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

No further doses of study intervention will be administered to participants who meet any of the following permanent treatment discontinuation conditions at any time during the study treatment period:

- Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria (see Section 7.1.1)
- ECG: Meets any of the protocol-defined QTc stopping criteria (see Section 7.1.2)
- Pregnancy: Positive pregnancy test (see Section 8.4.5)
- Severe allergic reaction/anaphylaxis: Participants with severe allergic reaction/anaphylaxis with no clear alternative cause (see Appendix 8)
- Vasculitis: Participants with confirmed vasculitis or suspected vasculitis with no alternative explanation (see Section 7.5).
- Study treatment unblinded: Unblinding of the study treatment assigned to a participant (see Section 6.4.2).

If a participant meets any of the treatment discontinuation conditions or chooses (for any reason) not to receive another dose of study intervention before the end of the protocol specified randomised intervention period:

- The investigator will make every effort to encourage the participant to remain in the study **and** to continue with all remaining study visits, including the Exit and Follow-up Visits.
- The primary reason for discontinuation of study intervention (e.g., AE, lack of efficacy, protocol deviation, investigator discretion, consent withdrawn etc.) must be recorded in the eCRF.
- Participants will be provided with the option to continue their scheduled visits in-clinic, at home, or by phone. The required study assessments will depend on whether the participant is attending the visit in-clinic, at home, or by phone. At a minimum, an assessment of exacerbations, AEs, SAEs, and concomitant medications will be completed.
- If for any reason, the participant later chooses to withdraw from the study, a Withdraw from Study Visit (see Section 7.2) should be conducted according to the SoA (Section 1.3).

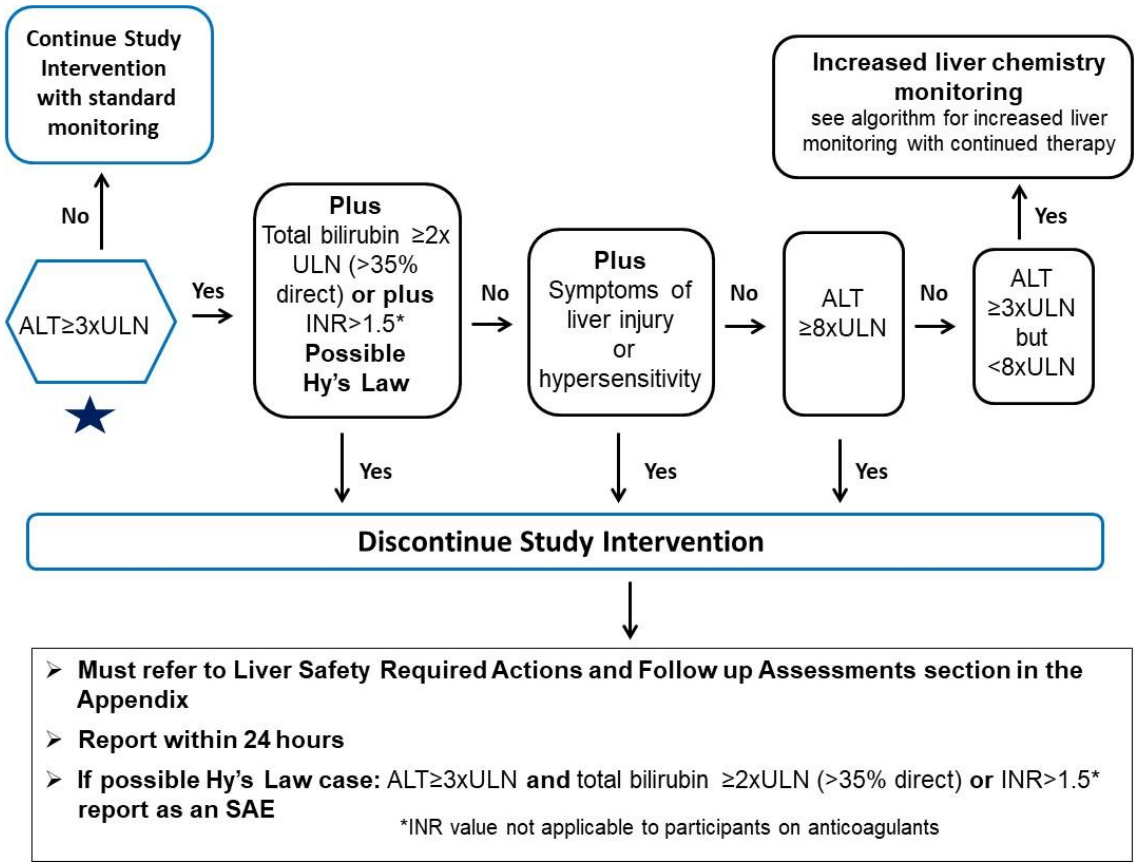
7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping criteria, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, the investigator believes that it is in the best interest of the participant.

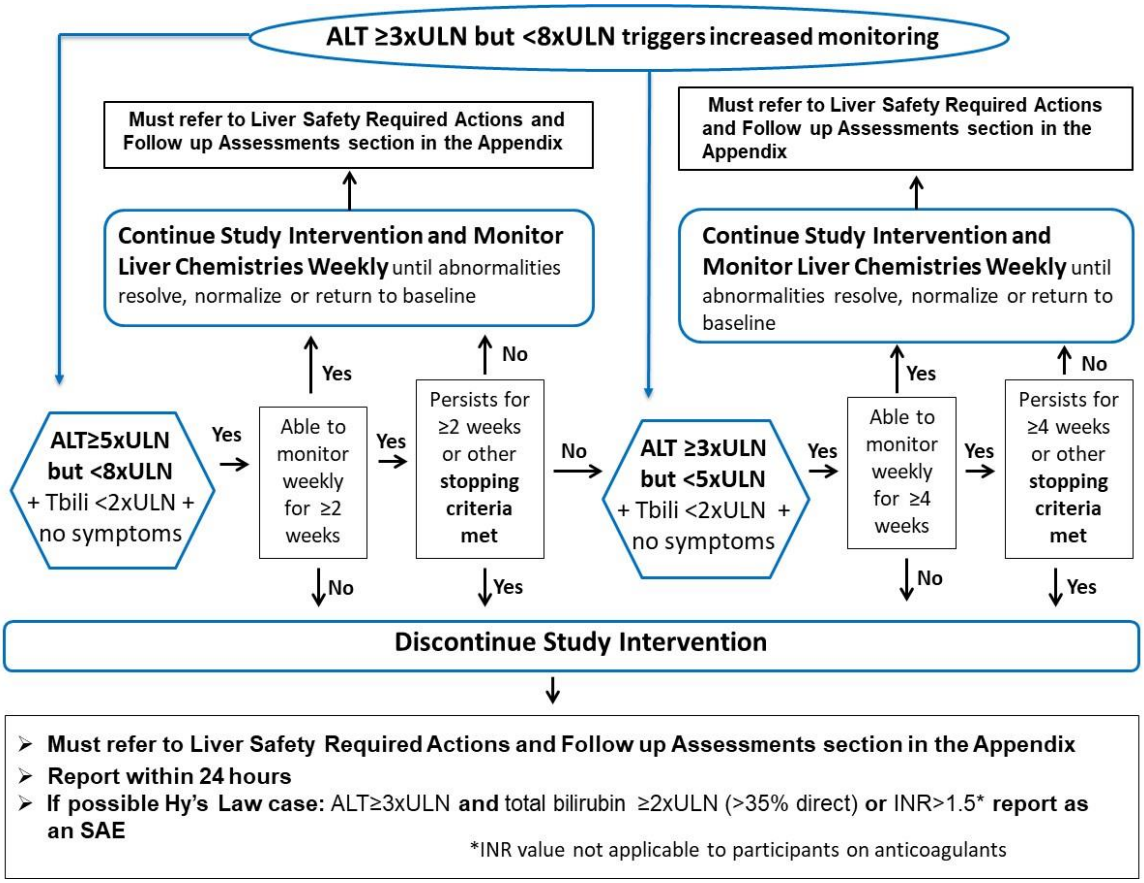
Liver Chemistry Stopping Criteria Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalised ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin

Refer to Appendix 6 for required Liver Safety Actions, Monitoring, and Follow-up Assessments.

Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT ≥3xULN but <8xULN and do not meet any of the liver stopping criteria



Abbreviations: ALT = alanine transaminase; Tbili = total bilirubin; INR = international normalised ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin.

Refer to Appendix 6 for required Liver Safety Actions, Monitoring and Follow-up Assessments.

7.1.1.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by a participant in this study will not be permitted.

7.1.2. QTc Stopping Criteria

Details on performing ECG assessments can be found in Section 8.3.3.

The QT interval corrected using Fridericia's formula (QTcF) must be used for *each individual participant* to determine eligibility for and discontinuation from the study intervention. This formula may not be changed or substituted once the participant has been enrolled.

For this study, the following QTc stopping criteria will apply:

- QTcF >500 msec OR uncorrected QT >600 msec
- Change from baseline of QTcF >60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTcF with Bundle Branch Block	**Discontinuation QTcF with Bundle Branch Block**
<450 msec	>500 msec
450 – 480 msec	≥530 msec

The QTcF value from the 12-lead ECG central over-read at randomisation Visit 2 should be used as baseline QTcF value for any changes from baseline calculations during the study. After randomisation 12-lead ECG central over-read values should be used to assess QTc stopping criteria, with the exception of Visit 10 (Week 26) where 12-lead ECG machine read values should be used.

7.1.3. Temporary Discontinuation

For this study, a temporary discontinuation refers to a delayed administration of the second dose of study intervention at Week 26.

If a participant becomes infected (parasitic infection) during the study intervention period before receiving the second dose of study intervention and does not respond to anti-helminth treatment, a delayed administration of the study intervention may be considered in consultation with the GSK Medical Monitor.

7.2. Participant Discontinuation/Withdrawal from the Study

- Participants are strongly encouraged to remain in the study for the entire duration but may prematurely withdraw from the study at any time at his/her own request, at the request of their legally authorised representative (LAR), or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.
- Participants who prematurely withdraw from the study should attend:
  - a Withdraw from Study (WS) Visit, 26 weeks after the last administered dose of study intervention (at Week 26 or Week 52) **AND**
  - a Follow-up visit/call, 30 weeks after the last administered dose of study intervention for AE/SAE and pregnancy assessments.

  Note: this includes any participants who initially discontinue study intervention and remain in the study (Section 7.1) but later decide to withdraw from the study.

- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits (or scheduled phone calls, if applicable) and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study. A final attempt will be made to contact the participant for a safety follow-up 30 weeks after the last administered dose of study intervention.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

7.4. Reasons for Study Intervention Discontinuation and/or Study Withdrawal

The primary reason for study intervention discontinuation and/or study withdrawal will be recorded in the eCRF. When a participant withdraws consent, the investigator must document the reason (if specified by the participant) in the eCRF.

7.5. Criteria for Follow-up of Potential Type III Hypersensitivity (Immune Complex Disease /Vasculitis)

Owing to the adverse findings of arterial inflammation that were observed in the 1-month, but not 6-month, nonclinical toxicology studies, events potentially representing type III hypersensitivity/immune complex disease/vasculitis should be promptly reported to GSK, and consultation with the Medical Monitor is encouraged. Treatment for the event will be given as medically required. If possible, PK, ADA, C3, and C4 samples

may be taken at the time of the event along with haematology, clinical chemistry and urinalysis.

Symptoms potentially suggestive of vasculitis include but are not limited to:

- persistent* fever (*where persistent is considered to be a duration of ≥2 days)
- persistent* muscle and joint pain
- persistent* rash
- persistent* fatigue
- symptoms of peripheral neuropathy, like numbness or weakness
- laboratory abnormalities, e.g., decreased platelets, elevated creatinine, decrease in complement C3/C4, abnormal urinary albumin/creatinine ratio

Participants who experience any of the above events should be monitored until the event resolves and/or a diagnosis is established.

The symptoms and clinical features are often non-specific and heterogenous with respect to the time course over which they develop, organ involvement and the constellation of symptoms and severity. Early recognition of potential events of vasculitis is important to timely diagnosis and subsequent treatment.

The precise management will depend on the clinical evaluation at the time of presentation and ongoing assessment including consideration of relevant differential diagnoses. Given that there is often a differential for presenting symptoms such as infection, and indeed such factors may also precipitate immune related AEs, these factors (infectious, neoplastic, metabolic, toxic) should be given due consideration and ruled out.

Serological, immunological, and histological (biopsy) data should be considered to support the diagnosis and consultation with the GSK Medical Monitor, and an appropriate medical specialist should be considered when investigating a possible immune related AE.

Unscheduled PK, ADA, C3 and C4 samples may be taken at the time of the event and samples may be taken for additional biomarkers (e.g., antinuclear antibodies [ANA], anti-neutrophil cytoplasmic antibodies [ANCA]) in the setting of clinical concern regarding the possibility of immune complex disease. If necessary, testing for biomarkers, e.g., ANA, ANCA (anti-myeloperoxidase [MPO] antibody and anti-proteinase 3 [PR3] antibody), may also be conducted using the frozen baseline serum samples (that were collected and stored prior to administration of study intervention) to allow for evaluation of interval change for participants with suspected vasculitis (see Section 8.7.2). Other possible causative or differential factors for abnormal clinical or laboratory observations may also have to be investigated including testing to exclude infection.

If clinically indicated, the participant may be referred to a specialist for further management, which may include organ biopsy.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Section 1.3).
- As detailed in the SoA (Section 1.3), participants who are not entering the OLE study 212895 should make every effort to complete the Week 56 follow-up visit/call on the scheduled day. The visit may be completed within 7 days of the scheduled time-point.
- Every effort should be made to reduce missing data throughout the study.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue to receive the second scheduled dose of study intervention, if applicable.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilised for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Laboratory results that could unblind the study (e.g., haematology differential [absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes]) will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Participants should be provided a quiet space in which to complete patient-reported outcomes (PRO), prior to other assessments and procedures. Site staff can provide limited advice if required, however participants should not be guided or directed in answering questions. Family or friends should not influence the answers. Site staff should encourage participants to complete all questions.

8.1. Screening and Critical Baseline Assessments

8.1.1. Pre-screening Visit (Visit 0)

Informed consent should be obtained at the Pre-screening Visit or the Screening Visit, prior to initiating any study assessments. A participant number will be assigned at the time the ICF is signed. Participants can conduct the Pre-screening Visit (Visit 0) up to 2 weeks prior to the Screening Visit (Visit 1).

The pre-screening procedures will include a review/assessment of:

- Inclusion/exclusion criteria (see Section 5.1 and Section 5.2)
- Demographic information including gender, ethnic origin, race, and year of birth (can be conducted at Visit 1 instead, if necessary)
- Childbearing status for all women (can be conducted at Visit 1 instead, if necessary); for WOCBP, contraception should be started at least 14 days prior to receiving the first dose of study intervention (see Appendix 4)
- Therapy history and concomitant medications including maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications

All clinic visits from Pre-screening Visit 0 to the Exit Visit (or if applicable, the WS Visit or the Follow-up Visit) should be completed in the relevant eCRF form. Visit 1, 2, 10 and WS visit must be registered in the IRT.

Serious adverse events must be collected from signing of Informed Consent if considered related to study procedures.

8.1.2. Critical Assessments performed at Screening (Visit 1)

The following critical assessments will be conducted at Screening Visit 1:

- Review inclusion/exclusion criteria (see Section 5.1 and Section 5.2)
- Review therapy history and concomitant medications including maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications.
- Medical history including:
  - Asthma including current treatment, duration of asthma, courses of rescue CSs, history of previous intubations, asthma exacerbation history in previous year, asthma triggers
  - Cardiovascular (CV) medical history/risk factors (as detailed in the eCRF)
  - Vasculitis, allergies and anaphylaxis history
  - Smoking history and current status
  - Historical blood eosinophil count - participants without a documented blood eosinophil count ≥300 cells/µL in the 12 months prior to Screening Visit 1 must show a blood eosinophil count ≥150 cells/µL, based on the sample collected at Visit 1 (see randomisation criterion 1, Section 5.3.1). If the Screening Visit test result does not meet the blood eosinophil count eligibility criteria, the laboratory assessment may be repeated, at the discretion of the investigator, if it is judged to be likely in the eligible range for study inclusion within the run-in period prior to Visit 2.
- Spirometry including bronchodilator responsiveness testing using the Maximum Bronchodilator Procedure (see Section 8.2.3). If a patient fails the protocol-specified reversibility criterion or FEV_1 inclusion criteria, spirometry retest is allowed during the run-in period.

- PGI-S (see Section 8.2.8)
- Safety Assessments including:
  - Physical exam (see Section 8.3.1)
  - Vital signs (see Section 8.3.2)
  - Resting 12-lead ECG (see Section 8.3.3)
  - AE/SAE assessment
- Blood/urine sample collection for the following laboratory tests (see Section 8.3.4):
  - Haematology with differential
  - Clinical chemistry (including liver chemistry)
  - Serum pregnancy test – for all WOCBP (childbearing potential for all women will be assessed at pre-Screening) (see Section 8.3.5)
  - Urinalysis (can be conducted at Visit 2 instead, if necessary)
  - Parasitic screening (only in regions with high-risk or for participants who have visited a high-risk region in the past 6 months)
- eDiary registration and training
- Provide medical problems and healthcare utilisation worksheet (see Section 8.9)
- Complete ADSD/ANSD (to be completed daily at home; see Section 8.2.10)

8.1.3. Critical Assessments performed at Randomisation (Visit 2)

The following critical assessments will be conducted at randomisation Visit 2:

Review of randomisation criteria (see Section 5.3), and data collected at Visit 1, including, if applicable, verification that the asthma-related peripheral blood eosinophil count is ≥150 cells/μL, based on the sample collected at Visit 1

- Review of concomitant medications
- Spirometry (if airway reversibility was not demonstrated at Visit 1, the Maximum Bronchodilator Procedure may be repeated at Visit 2) (see Section 8.2.3)
- SGRQ (see Section 8.2.4)
- ACQ-5 (see Section 8.2.5)
- SNOT-22 (see Section 8.2.7)
- Review eDiary asthma symptoms and PEF summary report
- PGI-S (see Section 8.2.8)
- Safety assessments including:
  - Vital signs (see Section 8.3.2)

  - Resting 12-lead ECG (see Section 8.3.3)
  - AE/SAE assessment

- Blood/urine sample collection for the following laboratory tests (see Section 8.3.4):
  - Haematology with differential
  - Total IgE
  - Clinical chemistry (including liver chemistry)
  - Urine pregnancy test – for all WOCBP (see Section 8.3.5)
  - Complement C3 and C4
  - PK (see Section 8.5)
  - Baseline immunogenicity (see Section 8.8)
  - Storage of a baseline sample that may be analysed for the presence of ANCA (anti-MPO antibody and anti-PR3 antibody tests), ANA, and anti-dsDNA antibody, if necessary (see Section 7.5)
  - Storage of a baseline sample (with the participant's consent and where permitted) that may be analysed for exploratory biomarkers (see Section 8.7.3)
- Provide and review medical problems and healthcare utilisation worksheet (see Section 8.9)

The following items will be completed at home:

- PROMIS Items (see Section 8.2.6)
- Complete ADSD/ANSD daily (see Section 8.2.10)

8.2. Efficacy Assessments

8.2.1. Efficacy Endpoints

Efficacy endpoints and estimands are provided in Section 3.

8.2.2. Asthma Exacerbations

Clinically significant exacerbations of asthma are defined by:

Worsening of asthma which requires use of systemic CSs[1] and/or hospitalisation and/or Emergency Department (ED) visit.

[1]*For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.*

Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

Details of each asthma exacerbation, including medications used to treat exacerbations should be recorded in the eCRF.

Asthma exacerbations should not be recorded as an AE unless they meet the definition of a SAE.

The time period for collection of exacerbation information in the eCRF will be from the start of study intervention until the Exit Visit or Follow-up Visit if applicable.

8.2.3. Pulmonary Function Testing/ Spirometry

Spirometry lung function assessments will be performed for all participants at specified visits to assess $FEV_{1.}$ At least 3 valid spirometry efforts should be attempted (with no more than 8 attempts) using the ATS guidelines [Miller, 2005]. Spirometry includes FEV_1, percent predicted FEV_1, Forced Vital Capacity (FVC) and FEV_1/FVC. Spirometry assessments will be performed at screening (Visit 1), randomisation (Visit 2), and at scheduled in-clinic visits according to the SoA (Section 1.3). At each visit, spirometry should be performed at the same time of day (±1 hour) as the assessment performed at Visit 2 (the baseline assessment). Participants should try to withhold short-acting beta-2-agonists (SABAs) for ≥6 hours and LAMAs/LABAs for ≥12 hours prior to the clinic visit, if possible.

Spirometry should not be conducted for participants with confirmed/suspected COVID-19.

8.2.3.1. Reversibility using the Maximum Post-Bronchodilator Method

Pre-bronchodilator measurements will be taken at the clinic visits specified in the SoA (Section 1.3): at screening, randomisation, Week 26 Visit, and Exit Visit (or EW Visit). In addition, post-bronchodilator values will be recorded following reversibility testing using the Maximum Post-Bronchodilator Method. Participants' reversibility will be assessed at Visit 1 (Screening). For participants unable to achieve ≥12% reversibility and 200 mL change at Visit 1, reversibility can be repeated at Visit 2 to confirm eligibility for the study (see randomisation criterion 2, Section 5.3.1). The procedures involved in the Maximum Post-Bronchodilator Method are those generated by the Pulmonary Physiology Subcommittee [Tepper, 2012]. Additional details on the reversibility testing procedures using the Maximum Post-Bronchodilator Method can be found in the spirometry section of the SRM.

8.2.4. St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a well-established instrument, comprising 50 items designed to measure Quality of Life in participants with diseases of airway obstruction [Jones, 1992]. The questionnaire will be administered as per guidance from the measure developers and completed electronically according to the SoA (Section 1.3).

8.2.5. Asthma Control Questionnaire-5 (ACQ-5)

The ACQ-5 is a five-item questionnaire, which has been developed as a measure of participants' asthma control that can be quickly and easily completed [Juniper, 2005].

The questions are designed to be self-completed by the participant. The five questions enquire about the frequency and/or severity of symptoms (nocturnal awakening on waking in the morning, activity limitation, and shortness of breath, wheeze) over the previous week. The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. This will be completed electronically according to the SoA (Section 1.3).

8.2.6. PROMIS Fatigue Items

The PROMIS Fatigue Item Bank includes a number of items assessing concepts from mild tiredness to exhaustion [Christodoulou, 2008; Cella, 2016]. A small number of individual questions assessing the concept of "Energy" from the PROMIS Fatigue item bank will be administered. Participants will complete these items on an electronic handheld device.

The PROMIS fatigue items should only be administered to participants for whom an appropriate translation is available (see the SRM for further details).

8.2.7. Sino-nasal Outcomes Test-22 (SNOT-22)

The SNOT-22 is a 22-item self-administered questionnaire to measure disease-specific quality of life of chronic rhinosinusitis (with or without nasal polyposis). The SNOT-22 contains questions about a broad range of health and HRQoL problems including physical problems, functional limitations and emotional consequences. The questions are designed to be self-completed by the participant [Hopkins, 2009]. The participant is asked to rate the severity of each item over the previous 2 weeks on a scale from 0 (no problem) to 5 (problem as bad as it can be). Responses to the questionnaire will be captured electronically.

The SNOT-22 questionnaire should only be administered to participants for whom an appropriate translation is available (see the SRM for further details).

8.2.8. Patient Global Impression of Asthma Severity/Change (PGI-S, PGI-C)

Patient Global Impression of Asthma Severity (PGI-S): The participant will complete a PGI-S question at Randomisation and visits according to the SoA (Section 1.3). This single global question will ask participants to rate their asthma severity on a five-point scale (no symptoms, mild, moderate, severe, very severe). Responses will be captured electronically.

Patient Global Impression of Change (PGI-C) from Baseline of Asthma Severity: The participant will complete a PGI-C question from baseline of their asthma severity at the visits specified in the SoA (Section 1.3). The single question will ask participants to rate the overall change in their asthma severity compared with Day 1 (randomisation) prior to start of study intervention. The rating will use a five-point scale (much better, a little better, no change, a little worse, much worse) and responses will be captured electronically.

The PGI-S/PGI-C questionnaire should only be administered to participants for whom an appropriate translation is available. Additional instructions will be provided in the SRM.

8.2.9. Clinician/Patient Rated Response to Therapy

This is an overall evaluation of response to treatment, conducted separately by the investigator and the participant using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse

The evaluations will be completed electronically at the visits specified in the SoA (Section 1.3).

8.2.10. Asthma Daily Symptom Diary/Asthma Nightly Symptom Diary (ADSD/ANSD)

The ADSD/ANSD is a 6-item self-administered patient-reported diary developed by the PRO Consortium's Asthma Working Group (in accordance with the Food and Drug Administration's PRO Guidance) to facilitate comprehensive and reliable assessment of asthma symptoms from a patient's perspective [Gater, 2016].

The ADSD/ANSD is intended for use by adults and adolescents (aged 12 years and older) who are diagnosed with asthma to rate the severity of their symptoms in the three core categories: breathing symptoms (wheezing, shortness of breath), chest symptoms (chest tightness, chest pain) and cough.

The ADSD/ANSD must be completed twice daily by the participant:

- ADSD is to be completed before going to bed and refers to asthma symptoms during the day.
- ANSD is to be completed upon waking and refers to asthma symptoms during the previous night.

Participants are required to rate the six symptoms at their worst during the respective timeframes using an 11-point numeric rating scale (NRS) ranging from 0 ('None') to 10 ('As bad as you can imagine'). Responses will be captured electronically.

The ADSD/ANSD questionnaire should only be administered to participants for whom an appropriate translation is available. Further details are contained in the SRM.

8.2.11. eDiary Asthma Parameters and Alerts

The participant will be asked to record the following parameters daily in the eDiary from Visit 1 onwards:

- Morning peak expiratory flow (best of three), before rescue medication usage (L/min).
- Occasions of rescue usage over the previous 24-hours.
- Asthma symptom score over the previous 24-hours using a 6-point scale (Appendix 9).
- Frequency of awakening due to asthma symptoms requiring rescue medication use.

For safety the following alerts, indicative of worsening asthma, will be programmed into the eDiary with instructions to contact the investigator if any of the alert criteria are met. An alert in itself will not qualify as a clinically significant exacerbation:

- Decrease in morning PEF ≥30% on at least two of three successive days, compared with baseline (last 7 days of run-in).
- An increase of ≥50% in rescue medication on at least two of three successive days, compared with the average use for the previous week.
- Awakening due to asthma symptoms requiring rescue medication use for at least two of three successive nights.
- A symptom score of 5 for at least two of three successive days.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3) – where possible, these should be aligned with standard of care.

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Eyes, CV, Respiratory, Gastrointestinal and Neurological systems. Height (screening only) and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

- Temperature, pulse rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the resting state with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and should be taken before blood collection for laboratory tests.

8.3.3. Electrocardiograms (ECGs)

- Twelve-lead ECGs will be obtained at the time points specified in the SoA (see Section 1.3) using an ECG machine, provided by GSK via a designated central laboratory, that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- The QTcF formula must be used for *each* individual participant to determine eligibility. This formula may not be changed or substituted once the participant has been enrolled. Refer to Section 7.1.2 for the QTcF formula.
- If an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTcF values of the three ECGs to determine whether the participant should be screened/ randomised/ discontinued from the study intervention (but not from the study). Refer to Section 5.2 and Section 5.3.2 for exclusion/randomisation exclusion criteria related to ECG assessment and Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- ECG measurements will be made after the participant has rested in the supine position for 5 minutes. The ECG should be obtained after the vital signs assessments but before lung function testing followed by other study procedures. Collection shortly after a meal or during sleep should be avoided since QT prolongation can occur at these times.
- Paper ECG traces will be recorded at a standard paper speed of 25 mm/sec and gain of 10 mm/mV, with a lead II rhythm strip. There will be electronic capture and storage of the data by a validated method.
- Paper ECG traces are required to be maintained at the site with other source documents.

8.3.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and refer to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study until the Exit Visit (or Follow-up visit/call if applicable) should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or Medical Monitor. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified, and the Sponsor notified.

- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- To maintain the treatment blind, the site and the central study team will not be sent information on haematology differential (absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes) from any visits post-randomisation.

8.3.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- A serum pregnancy test should be conducted for all WOCBP at the screening visit (Visit 1) and the Exit visit. In addition, a urine pregnancy test should be performed for all WOCBP prior to randomisation (Visit 2), on a monthly basis at the specified scheduled study visit, and at the Follow-up Visit/call (if applicable) as per the SoA (Section 1.3).
- A final urine pregnancy test should be conducted for all WOCBP, 30 weeks after the last administered dose of study intervention:
    - Participants who enter the OLE study will have a urine pregnancy test prior to receiving the first dose of open-label GSK3511294.
    - Participants who do not enter the OLE study should have a urine pregnancy test at the Follow-up Visit/call (Week 56). A self-reported home urine pregnancy test result is acceptable if the follow-up is conducted as a phone call visit.
    - Participants who withdraw early from the study should have a urine pregnancy test, 4 weeks after the WS Visit (see Section 7.2).
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Section 10.3. Asthma exacerbations should not be recorded in the AE section of the eCRF unless they meet the definition of a SAE.

The definitions of device-related safety events, (adverse device effects [ADEs] and serious adverse device effects [SADEs]), can be found in Section 10.7. Device deficiencies are covered in Section 10.7.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of intervention (Visit 2) until the Exit Visit or follow-up visit/call (if applicable) at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the Exit Visit or the follow-up visit/call (if applicable) at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions (in the eCRF) not as AEs.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to GSK within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify GSK.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 8.4.7), will be followed until the event is resolved,

stabilised, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to GSK of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from GSK will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and GSK policy and forwarded to investigators as necessary.

8.4.5. Pregnancy

- Any female participant who becomes pregnant while participating in the study will not receive another dose of study intervention.
- Details of all pregnancies in female participants will be collected from the start of study intervention and until 30 weeks after the last administered dose of study intervention.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within **24 hours** of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

8.4.6. Cardiovascular and Death Events

For any CV events detailed in Appendix 3 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV CRF pages are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific CV section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF page is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.4.7. Adverse Events of Special Interest

Adverse events of special interest (AESI) include:

- Allergic reactions including anaphylaxis

  Note: these events will be assessed by the investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006] (Appendix 8).

- Type III hypersensitivity (immune complex disease/vasculitis) reactions
- Local injection site reactions
- QTc prolongation

See Section 2.3.1 for additional details.

8.4.8. Medical Device Deficiencies

Medical devices (PFS) are being provided for use in this study as a delivery method for GSK3511294 or matching placebo injections. To fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device Deficiency can be found in Section 10.7.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 10.3 of the protocol.

8.4.8.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- The method of documenting Medical Device Incidents is provided in Section 10.7.

8.4.8.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.8.3. Prompt Reporting of Medical Device Deficiencies to Sponsor

- Device deficiencies will be reported to the Sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.
- The Medical Device Deficiency Report Form will be sent to the Sponsor by email. If email is unavailable, then fax should be utilised.
- The Sponsor will be the contact for the receipt of device deficiency reports.

8.4.8.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all deficiencies occurring with any medical device provided for use in the study in order for the Sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.5. Pharmacokinetics

- Blood samples will be collected for measurement of plasma concentrations of GSK3511294 as specified in the SoA (Section 1.3).
- The actual date and time (24-hour clock time) of each sample will be recorded. Samples obtained at Visit 2 (Week 0) and Visit 10 (Week 26) should be drawn prior to dosing.
- Collection, processing, storage and shipping procedures are provided in the central laboratory manual.
- Intervention concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6. Genetics and Pharmacogenomics

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Section 10.5. Genetics and Pharmacogenomics for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the central laboratory manual. Country specific requirements are specified in the SRM.

8.7. Biomarkers/ Pharmacodynamic Markers

8.7.1. Blood Eosinophil Counts

In order to investigate the PD effects of GSK3511294, blood eosinophil counts will be measured as part of the standard haematological assessments according to the SoA (Section 1.3). The site staff and central study team will be blinded to each participant's blood eosinophil count (as well as overall haematology differential [absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes]) from all post-randomisation blood tests. Total white blood cell counts will be available throughout the study.

8.7.2. Complement, IgE, and Inflammatory Markers

Blood samples will be collected to measure complement (C3 and C4) and total IgE, according to the SoA (Section 1.3).

A baseline serum sample will be collected at Visit 2 and stored. If necessary, this sample may be analysed for the presence of ANCA (using anti-MPO antibody and anti-PR3 antibody tests), and ANA, including anti-dsDNA antibodies. After dosing, additional inflammatory markers and tests may be considered on an ad-hoc basis should there be clinical concerns regarding an immune-mediated AE (see Section 7.5).

8.7.3. Exploratory Biomarkers

With the participant's consent and where permitted, a serum sample for exploratory biomarkers will be collected as specified in the SoA (Section 1.3). The samples will be stored after collection and may be analysed for any biomarkers that are thought to play a role in GSK3511294 response, asthma or related diseases, or to evaluate their association with observed clinical responses to GSK3511294. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to GSK3511294.

Participation in exploratory biomarker research is optional. Participants who do not wish to participate in the exploratory biomarker research may still participate in the study. Country specific requirements are specified in the SRM.

8.8. Immunogenicity Assessments

Antibodies to GSK3511294 will be evaluated in serum samples collected from participants according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the Exit Visit or the final in-clinic visit for participants who withdraw early from the study. Processing, storage and shipping procedures are provided in the SRM.

In the immunogenicity assessment for GSK3511294, a tiered analyses approach will use a validated binding ADA assay (screening, confirmation and titration assays) and a validated neutralisation antibody (NAb) assay. If necessary, further immune response characterisation may be performed as needed.

8.9. Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation data, associated with medical encounters, will be collected by the investigator and study-site personnel for all participants throughout the study. The data will be collected using a medical problems and healthcare utilisation worksheet according to the SoA (Section 1.3). Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to evaluate the effect of GSK3511294 on health care resource utilisation for asthma including hospitalisation, ED visits, and physician office/clinic visits.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary study objective is to test for the superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC, assessed by the annualised rate of clinically significant exacerbations measured over the study intervention period of 52 weeks.

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 and placebo.

9.2. Sample Size Determination

Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125).

9.2.1. Sample Size Assumptions

A sample size of 375 participants (2:1 GSK3511294 to placebo allocation ratio) is based on sufficient power to conclude superiority on primary and key secondary endpoints.

9.2.1.1. Primary Endpoint

The assumed true annualised rate of exacerbations in the placebo arm is 1.18. Based on an assumed true treatment difference of a 50% reduction in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC, a sample size of 375 randomised participants (250 to GSK3511294, 125 to placebo) will provide 99% power for the primary endpoint at a 5% two-sided significance level [PASS, 2020].

The assumptions for the placebo rate and treatment effect are median values from an elicitation exercise which used Phase 3 anti-IL-5/5R historical data (~50% reduction in exacerbations) and expert opinion. The sample size is based also on an assumption of 0.8 for the dispersion parameter which was observed in two mepolizumab studies [Pavord, 2012; Ortega, 2014]. It was assumed that 14% of participant-years data will be missing due to study withdrawal, which is also consistent with mepolizumab studies.

Based on the assumptions above, the minimum observed treatment difference estimated to result in significance at the 5% two-sided significance level is a 27% reduction in exacerbations for GSK3511294 + SoC compared with placebo + SoC (rate ratio of 0.73).

9.2.1.2. Secondary Endpoints

Table 3 describes the assumptions and power values for two key secondary endpoints. The assumptions are obtained from the Phase 3 mepolizumab studies [Pavord, 2012; Ortega, 2014; Chupp, 2017].

Table 3 Power Calculations for Key Secondary Endpoints

Endpoint	Assumed treatment difference (GSK3511294 + SoC vs. placebo + SoC)	Standard deviation	Power
Change from baseline in SGRQ total score at Week 52	-7	17	96%
Change from baseline in ACQ-5 score at Week 52	-0.35	1.1	83%

9.2.2. Sample Size Sensitivity

The sample size and power calculations are based on assumptions about the true values for parameters. The power of the study is dependent on changes in these assumptions, in particular the assumed annualised exacerbation rates. Table 4 illustrates how changes in assumptions for two parameters (placebo + SoC annualised exacerbation rate and treatment effect) affect the power.

Table 4 Estimates of Power for Assumed Placebo + SoC Exacerbation Rate and Assumed Percent Reduction with GSK3511294 + SoC Compared with Placebo + SoC

Percent reduction in annualised exacerbation rate with GSK3511294 + SoC vs. placebo + SoC	Placebo + SoC annualised exacerbation rate			
	1.0	1.1	**1.18**	1.3
30%	61	63	65	67
40%	88	90	91	92
50%	98	99	**99**	99

9.3. Analysis Sets

For the purpose of analyses, the following populations are defined:

Population	Description
Screened	All participants who sign the ICF.
Enrolled	All participants who entered the study. Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.

Randomised	All participants who were randomly assigned to study intervention in the study.
Full Analysis Set (FAS)	All randomised participants who receive at least one dose of study intervention. Participants will be analysed according to the intervention they are allocated at randomisation. This population will serve as the primary population for analyses of efficacy endpoints.
Safety	All randomised participants who receive at least one dose of study intervention. Participants will be analysed according to the intervention they are allocated at randomisation, unless a participant receives a different intervention to the randomised intervention at all protocol-defined administrations, in which case the participant will be analysed according to the actual intervention they received. This population will serve as the primary population for analyses of safety endpoints.

Further populations to be used for other assessments will be defined in the statistical analysis plan (SAP).

9.4. Statistical Analysis

The SAP will be finalised prior to un-blinding and it will include a more technical and detailed description of the statistical analyses described in this section.

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC.

9.4.2. Primary Endpoint

9.4.2.1. Main Estimand

Target Participant Population	Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.
Primary Endpoint	Annualised rate of clinically significant exacerbations over 52 weeks. Clinically significant exacerbations are defined in Section 8.2.2.
Intercurrent events and strategies	The anticipated key intercurrent events and corresponding strategies are: a) Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring

	b) Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred c) Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring
Summary measure	Ratio of the rates of exacerbations between GSK3511294 + SoC and placebo + SoC.
Analysis Method	The primary analysis of the annualised rate of clinically significant exacerbations will use a negative binomial model. Covariates included will be baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high dose, see Appendix 10), region, number of exacerbations in the year prior to the study, baseline % predicted FEV_1 and treatment group with $\log_e$(time in study in years) as an offset variable. The rate ratio and 95% confidence interval (CI) will be provided for the comparison between GSK3511294 + SoC and placebo + SoC.
Handling of missing data and intercurrent events leading to exclusion of data	Missing data or data excluded due to intercurrent events will be handled as follows: • For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed "missing at random" (MAR) (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the primary endpoint, the data for the period following withdrawal will be assumed MAR (based on all data included in the analysis under the current estimand strategy). **Sensitivity analyses** will be conducted to investigate the conclusions from deviations from these assumptions regarding missing data for (b) above. Missing data for participants will be based on data from participants who have discontinued study intervention (off-treatment) but remained in the study [Roger, 2019]. A tipping point analysis will also be conducted that will impute missing data based on a plausible range of values for the rate of exacerbations per year. The imputed exacerbation rates will be varied independently for treatment arms. Further details will be provided in the SAP.

9.4.3. Secondary Endpoints

9.4.3.1. Main Estimands

Target Participant Population	Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.
Secondary Endpoints	• Change from baseline in SGRQ total score at Week 52 • Change from baseline in ACQ-5 score at Week 52

	• Change from baseline in pre-bronchodilator FEV_1 at Week 52
Intercurrent events and strategies	The anticipated key intercurrent events and corresponding strategies: a) Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring. b) Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred. c) Change in maintenance therapy or use of prohibited medications (listed in Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring
Summary measure	Difference in means between GSK3511294 + SoC and placebo + SoC.
Analysis Method	The analysis will be performed using a repeated measures mixed model. Covariates included will be baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high dose, see Appendix 10), number of exacerbations in the year prior to the study, baseline % predicted FEV_1,treatment group and visit, plus interaction terms for visit by baseline and visit by treatment group. The difference in means and 95% CI will be provided for the comparison between GSK3511294 + SoC and placebo + SoC.
Handling of missing data and intercurrent events leading to exclusion of data	Missing data or data excluded due to intercurrent events will be handled as follows: a) For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). b) For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy). **Sensitivity analyses** will be conducted to investigate the conclusions from deviations from these assumptions regarding missing and excluded data for (b) above. Missing data for participants will be based on data from participants who have discontinued study intervention (off-treatment) but remained in the study [Roger, 2019]. A tipping point analysis will also be conducted that will impute missing data based on a plausible range of means. The imputed means will be varied independently for treatment arms. Further details will be provided in the SAP.

The annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks will be evaluated using the same strategy as that described for the primary endpoint (see Section 9.4.2).

9.4.4. Other Endpoints

Full details of analysis methods to be used for other endpoints will be provided in the SAP.

9.4.5. Safety Analyses

All safety analyses will be performed on the Safety Population. Summaries of data will report data according to the nominal visit for which it was recorded. Occurrence of AEs, SAEs, AESIs, laboratory data, vital signs, and ECGs will be included in data displays in the form of listings, frequency tables, summary statistics, graphs, and statistical analyses where appropriate.

Adverse Events (AEs) will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and will be grouped by system organ class (SOC). AEs will be summarised by frequency and percentage of participants, by SOC and preferred term within each treatment group. Separate summaries will be presented for all AEs, drug-related AEs, serious AEs (SAEs), AEs leading to permanent discontinuation of study intervention or withdrawal from study and for any AEs of special interest.

9.5. Multiple Testing Strategy

The treatment comparison of interest for the primary and secondary endpoints is GSK3511294 100 mg SC + SoC vs placebo + SoC. A fixed sequence hierarchical testing procedure will be used to provide strong control of Type I error for multiplicity arising from the primary and multiple secondary endpoints. This will be carried out using a stepdown closed testing procedure where inference for an endpoint in the predefined hierarchy will be dependent on statistical significance having been achieved for the previous endpoints in the hierarchy. For example, for the primary endpoint, GSK3511294 + SoC will be compared to placebo + SoC at a two-sided 5% level. The next endpoint in the hierarchy (i.e. the first secondary endpoint) will be tested only if the test for the primary endpoint is significant at the two-sided 5% level. Testing will continue down the hierarchy for the remaining endpoints in an equivalent manner only if the previous endpoint in the hierarchy achieves statistical significance.

The hierarchy of the primary and secondary endpoints to be tested is as follows:

1. Annualised rate of clinically significant exacerbations over 52 weeks
2. Change from baseline in SGRQ at Week 52
3. Change from baseline in ACQ-5 at Week 52
4. Change from baseline in clinic pre-bronchodilator FEV_1 at Week 52
5. Annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

9.6. Interim Analysis

An unblinded interim analysis for futility will be performed by an statistical data analysis centre (SDAC) in conjunction with an IDMC to maintain study integrity. The futility analysis will not increase the type 1 error rate. Full details of the timing, operating

characteristics and stopping boundary will be included in a statistical analysis plan and/or IDMC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide GSK with sufficient, accurate financial information as requested to allow GSK to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or their legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- For participants 12-17 years old, written informed assent must be obtained in addition to the legally authorised representative(s)' consent. Assent will be obtained in accordance with applicable country or IRB/Ethics Committee regulations. Written informed consent will be obtained from participants turning 18 years of age to continue participation in the study.
- The medical record must include a statement that written informed consent/assent was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorised person obtaining the informed consent/assent must also sign the ICF.
- Participants must be re-consented/re-assented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their legally authorised representative.

Participants who are rescreened are required to provide consent/assent and sign a new ICF/assent form.

GSK (alone or working with others) may use a participant’s coded study data and samples and other information to carry out this study; understand the results of this study; learn more about GSK3511294 or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have GSK3511294 approved for medical use or approved for payment coverage.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by GSK. Any participant records or datasets that are transferred to GSK will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by GSK in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by

GSK, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

An Independent Data Monitoring Committee (IDMC) comprised of clinical experts external to GSK will review unblinded data at defined timepoints during the study. If deemed appropriate by the IDMC, or upon request by GSK or investigators, additional timepoints for review may be added.

Details of the structure and function of the IDMC, and analysis plan for IDMC reviews, are outlined in the IDMC Charter, which is available upon request.

In addition to the IDMC, the GSK SRT will review blinded safety data at regular intervals throughout the study to ensure participant safety, which includes safety signal detection at any time during the study. Details of the SRT process will be available in relevant SRT documents. The SRT will inform the IDMC if any safety signals are identified.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymised participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymised patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding

- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- GSK or a designee is responsible for the data management of this study including quality checking of the data.
- GSK assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of GSK. No records may be transferred to another location or party without written notification to GSK.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records

or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or

suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- GSK will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, GSK will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

All protocol required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).

Local laboratory results may be required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation to be performed – for example: when results from screening Visit 1 should be available before dosing on Visit 2, or at any time when a participant is unwell and results are required urgently.

If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded in the CRF.

To maintain the blind, the following data for post-randomisation samples will not be reported to investigators and blinded Sponsor representatives: absolute and percentage values of eosinophils, neutrophils, lymphocytes, monocytes, and basophils.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 5 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	**Parameters**			
Haematology[1]	Platelet Count	*RBC Indices:*	*WBC count with Differential: (post-dose results blinded as described in footnote 1)*	
	RBC Count	MCV	WBC	
	Haemoglobin	MCH	Neutrophils	
	Haematocrit	%Reticulocytes	Lymphocytes	
			Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry[2]	BUN	Potassium	AST(SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase[3]	Albumin
		Magnesium	GGT	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination and UACR (if blood or protein is abnormal [evidence of microalbuminuria or haematuria of ≥1+])			
Pregnancy testing	• Highly sensitive serum pregnancy test at Screening Visit 1 and Exit Visit; urine pregnancy tests for all other scheduled visits (as needed for WOCBP)[4]			
Other Screening Tests	• FSH and oestradiol (if required to confirm postmenopausal status) • Parasitic Screening (only required in regions with high-risk or for participants who have visited high-risk regions in the past 6 months). Sites should use local laboratories. • Total IgE • Serum samples collected at baseline will be frozen and stored for later analyses, if necessary: anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			

NOTES:
ALT = Alanine Aminotransferase; ANA = anti-nuclear antibody; AST = Aspartate Aminotransferase; BUN = Blood urea nitrogen; FSH = Follicle-stimulating hormone; GGT= gamma glutamyl transferase, MPO=myeloperoxidase; PR3=proteinase 3; SGOT = Serum Glutamic-Oxaloacetic Transaminase; SGPT = Serum Glutamic-Pyruvic Transaminase; UACR = urinary albumin-creatinine ratio; WBC = white blood cell; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

1. To maintain the treatment blind, the following data for post-randomisation samples will not be reported to investigators and blinded Sponsor representatives: absolute and percentage values of eosinophils, neutrophils, lymphocytes, monocytes, and basophils.
2. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Section 10.6 All events of ALT ≥3 × upper limit of normal (ULN) and total bilirubin≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalised ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported to GSK as an SAE.
3. If alkaline phosphatase is elevated, consider fractionating.
4. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention.

  NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalisation for signs/symptoms of the disease under study, death due to progression of disease, etc.).

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalisation or prolongation of existing hospitalisation • In general, hospitalisation signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AE. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. • Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalised ratio (INR) >1.5 must be reported as SAE
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; and both AE and SAE can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognised follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours and send/fax it to the Medical Monitor.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor or the SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Medical monitor or the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.
- Permanent sterilisation methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female
   A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   a) A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   b) Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

10.4.2. Contraception Guidance:

Female participants:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)c
• Bilateral tubal occlusion
• Azoospermic partner (vasectomised or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.

Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

• Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulationc
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulationc
  • oral
  • injectable

• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

Male participants: As GSK3511294 is a mAb that is not anticipated to interact directly with deoxyribonucleic acid (DNA) or other chromosomal material and minimal exposure through semen is expected, male participants will not be required to use contraception during the study.

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to GSK3511294 or asthma with an eosinophilic phenotype and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to GSK3511294 or study interventions of this drug class, and indication. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- Additional analyses of DNA samples may be conducted if it is hypothesised that this may help further understand the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to GSK3511294 or study interventions of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on GSK3511294 (or study interventions of this class) or asthma with an eosinophilic phenotype continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Required Actions, Monitoring and Follow-up Assessments

Liver Chemistry Stopping Criteria and Increased Monitoring Criteria are designed to assure participant safety and evaluate liver event aetiology.

Liver Chemistry Stopping criteria and Required Follow-up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** total bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5
Cannot Monitor	ALT ≥ 5xULN but <8xULN **and** cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN **and** cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions, Monitoring and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study intervention • Report the event to GSK **within 24 hours** • Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform follow-up assessments as described in the Follow-up Assessment column. • Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below) **MONITORING:** **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5:**	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis, within a week of meeting increased liver monitoring criteria.[5] • Obtain a serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin. • Fractionate bilirubin, if total bilirubin≥2xULN

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **For all other stopping criteria (total bilirubin <2xULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilise or return to within baseline **RESTART/RECHALLENGE** • **Do not restart/rechallenge** participant with study intervention since **it is not allowed per protocol;** continue participant in the study for any protocol specified follow-up assessments.	• Obtain complete blood count with differential to assess eosinophilia. This blood sample will be sent to the central laboratory to maintain the blind while study is ongoing. Results will be provided only if unblinding of a participant's treatment assignment is required. Also note that the mechanism of action of GSK3511294 leads to lowering of eosinophils. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications. • Record alcohol use on the liver event alcohol intake form **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease; complete Liver Imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance:

	○ In patients when serology raises the possibility of autoimmune hepatitis (AIH) ○ In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention ○ In patients with acute or chronic atypical presentation: • If liver biopsy conducted complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3xULN and total bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5 which may indicate severe liver injury (possible 'Hy's Law'), **must be reported to GSK as an SAE**; the INR threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: hepatitis A Immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. In those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal, 2005].
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the central laboratory manual.

Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** total bilirubin <2xULN or INR≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** total bilirubin <2xULN or INR≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention. • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) until they resolve, stabilise or return to within baseline. • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, (total bilirubin <2xULN and INR ≤1.5) continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and total bilirubin <2xULN and INR ≤1.5, monitor participants twice monthly until liver chemistries resolve or return to within baseline.

References

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

10.7. Appendix 7: AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the Sponsor will comply with all local medical device reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.1.1 for the list of GSK medical devices).

10.7.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• An AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. • An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. The term ‘life-threatening' in the definition of ‘serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe. • A permanent impairment of a body structure or a body function.

• Inpatient or prolonged hospitalisation. Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
c. Led to foetal distress, foetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.7.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

10.7.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/device deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.7.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor or the SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool

- Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the Medical Monitor or the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

10.7.6. Reporting of SADEs

SADE Reporting to GSK

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

10.8. Appendix 8: Anaphylaxis Criteria

Joint National Institute of Allergy and Infectious Disease (NIAID)/ Food Allergy and Anaphylaxis Network (FAAN) Second Symposium on Anaphylaxis [Sampson, 2006]. The criteria do not make a distinction based on underlying mechanism. These criteria are summarised as follows:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalised hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
   a) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a) Involvement of the skin-mucosal tissue (e.g., generalised hives, itch-flush, swollen lips-tongue-uvula)
   b) Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a) Adolescents (aged 12-17): low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

10.9. Appendix 9: Daily Asthma Symptom Score

Each morning, participants will record an asthma symptom score using the following scale:

Daily Symptom Score:

- 0 = No symptoms during the previous 24-hours.
- 1 = Symptoms for one short period during the previous 24-hours.
- 2 = Symptoms for two or more short periods during the previous 24-hours.
- 3 = Symptoms for most of the previous 24-hours which did not affect my normal daily activities.
- 4 = Symptoms for most of the previous 24-hours which did affect my normal daily activities.
- 5 = Symptoms so severe that I could not go to work/school or perform normal daily activities.

10.10. Appendix 10: Low, Medium and High Daily Doses of Inhaled Corticosteroids

Daily medium and high dose ICS options for adults and adolescents (12 years and older) are shown in Figure 1.

Figure 1 Low, medium and high daily doses of inhaled corticosteroids

Box 3-6. Low, medium and high daily doses of inhaled corticosteroids

This is not a table of equivalence, but instead, suggested total daily doses for the 'low', 'medium' and 'high' dose ICS options for adults/adolescents, p.54 and children 6–11 years, p.55, based on available studies and product information. Data on comparative potency are not readily available and therefore this table does NOT imply potency equivalence. Doses may be country-specific depending on local availability, regulatory labelling and clinical guidelines.

Low dose ICS provides most of the clinical benefit of ICS for most patients with asthma. However, ICS responsiveness varies between patients, so some patients may need **medium dose ICS** if their asthma is uncontrolled despite good adherence and correct technique with low dose ICS (with or without LABA). **High dose ICS** (in combination with LABA or separately) is needed by very few patients, and its long-term use is associated with an increased risk of local and systemic side-effects, which must be balanced against the potential benefits.

Adults and adolescents (12 years and older)			
Inhaled corticosteroid	**Total daily ICS dose (mcg) – see notes above**		
	Low	**Medium**	**High**
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (pMDI, extrafine particle*, HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle*, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	200		400
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400
Children 6–11 years – see notes above (for children 5 years and younger, see Box 6-6, p.153)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle*, HFA)	50-100	>100-200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80-160	>160
Fluticasone furoate (DPI)	50		n.a.
Fluticasone propionate (DPI)	50-100	>100-200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50-100	>100-200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100		200

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; n.a. not applicable; pMDI: pressurized metered dose inhaler (non-chlorofluorocarbon formulations); ICS by pMDI should preferably be used with a spacer. *See product information.

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- The medium to high dose for Japanese adolescent subjects 15 years or younger will be ≥200 µg/day of FP or other ICSs of equivalent dose) as per the Japanese asthma pediatric guidelines.
- Updates as per GINA 2021:
- Beclometasone dipropionate (pMDI, extrafine particle, HFA) changed to Beclometasone dipropionate (**DPI or** pMDI, extrafine particle, HFA)
- Budesonide (DPI) changed to Budesonide (DPI, **or pMDI, standard particle, HFA**)
- Mometasone Furoate (DPI) Low, Medium and High total daily ICS doses **reference to product information as it depends on DPI device.**

10.11. Appendix 11: Recommended Measures Related to COVID-19 Pandemic

Overall Rationale for this Appendix:

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the study intervention or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the study intervention or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

STUDY PROCEDURES DURING COVID-19 PANDEMIC

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrolment and treatment decisions for trial participants.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants.

- Clinical investigators should document in site files and in participant notes/Electronic Heath Records as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).

- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

- Spirometry should not be conducted for participants with confirmed/suspected COVID-19.

Protocol Defined Procedures/Visits:

- Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, measurement of vital signs and weight, and preparation and administration of study drug (at the discretion of the investigator). It is the

responsibility of the investigator to inform GSK when this occurs and to document in source notes.

- Remote visits may be performed at the participant's home by qualified study personnel or at a local medical facility, unless the investigator deems that a site visit is necessary.
- Additional unscheduled safety assessments such as routine blood sampling may be performed at the discretion of the investigator including in the participant's home, if deemed necessary. Biological samples may be collected at a different location, other than the study site (e.g., at participant's home) by qualified study personnel or at a local medical facility according to standard operating procedures and applicable regulations (see note). Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.
- If visits to a site/home are not feasible, then the medical evaluation of the participant's asthma may take place by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress. GSK will be accountable for working with the vendor to ensure the site has the required equipment, training and support for this model and should be notified as soon as possible by the investigator that the service is required.
- The study investigator is responsible for ensuring that the identification, management, and reporting of AEs and SAEs are completed in accordance with the protocol and applicable regulations. AEs are first reported by participants to the investigator/study team or may be identified by the study team during interactions with the participants via telemedicine encounters. In addition, mobile nurses may identify AEs as well and report them to the investigator for evaluation. Additionally, AEs may be identified from lab reports, imaging or ECG reports, and other records. As determined by the investigator, the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary.
- The participant should be informed of the plan and any potential risks associated with the virtual medium and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.
- The revised schedule of study activities is provided in Table 6.

Note: If the investigator wishes to conduct a trial visit at a location that has not been previously assessed by GSK, it is the investigator's responsibility to identify an adequate alternate location and to notify GSK of the alternate location. The investigator should ensure that this alternate location meets ICH GCP requirements, is well-equipped to perform study procedures and covered by an adequate insurance. Furthermore, the investigator should have sufficient oversight to ensure that the staff at the alternate location are trained to perform study procedures. Refer to and follow most recent local guidance and regulations if available or refer to FDA or EMA guidance available at time.

Study Intervention:

- If despite best efforts it is not possible to administer the dose of study intervention as defined in the protocol (see Section 6 Study Intervention and Concomitant Therapy), a maximum dose interval of 28 weeks may be used.
- In-clinic visits are required for administration of the study intervention (Week 0 and Week 26).
- In some cases, trial participants who no longer have access to study intervention or the investigational site may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment).

Data Management/Monitoring:

- The medical problems and healthcare utilisation worksheet may be transmitted from and to the investigator by electronic mail and or conventional mail. If copies/scans of the paper worksheet are sent to the investigator by electronic mail, the participant should be instructed to maintain the original documents and to return them to the site when a visit to the site will be allowed.
- If the eDiary device was provided to the participant, it may be returned to the site by conventional mail after the end of the relevant data collection period (Visit 17 Exit Visit).
- If on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a patient and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.
- eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilised during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK.

Assessments that can be Conducted Outside Clinical Study Site:

Activities/assessments that may be conducted outside of a clinical study site are indicated in Table 6.

- White boxes represent activities/assessments that are to be done during visits to the clinical study centre (pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 3, Visit 10, Visit 11, Exit Visit 17, and WS Visit if applicable).
- Grey boxes represent activities/assessments during study visits (Visits 4-9, Visits 12-16, and the FU Visit) that may be conducted by a home healthcare professional, where applicable country and local regulations and infrastructure allow (at the discretion of the investigator, based on safety and tolerability).
- The FU Visit may be conducted as a remote/home visit or as a phone call.
- During home visits, the scheduled collection of samples for laboratory and other assessments may be performed by a home healthcare professional.

Table 6 Schedule of Activities (SoA) Indicating Assessments that may be Conducted Outside of a Clinical Study Site

Protocol Activity	Pre-Screening	Screening/Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
General Eligibility Assessments																					
Informed consent [a]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote a.
Genetic sample informed consent [d]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote d.
Demography data collection	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; All females must be assessed at Visit 1 to determine childbearing potential.
Inclusion/Exclusion criteria	X	X																			
Historical blood eosinophil count		X																			See footnote e.
Medical history		X																			Include cardiovascular (CV), CV risk factors, asthma, exacerbations, vasculitis, allergies and anaphylaxis.
Smoking status		X																			
Parasite screening		X															X				Only required in regions with high-risk or for participants who have visited a high-risk region in the past 6 months. Use local laboratories for this test. For details refer to study reference manual (SRM).
eDiary registration and training		X																			Conduct thorough eDiary training at Screening Visit 1 and throughout the study on as-needed basis.

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Randomisation criteria			X																		Assess prior to randomisation; see footnote e.
Efficacy Assessments																					
Review for exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Collection of exacerbations at Visit 1 is historical data.
Spirometry (pre- and post-bronchodilator FEV_1)[h]		X	X								X							X	X		FEV_1=Forced expiratory volume in 1 second; Spirometry should not be conducted for participants with confirmed/suspected COVID-19 (see Section 8.2.3).
ACQ-5			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		ACQ-5=Asthma Control Questionnaire-5
Review eDiary (asthma symptoms, PEF summary)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PEF=Peak expiratory flow
HRQoL: PRO and Health Outcomes Assessments																					
SGRQ			X		X		X				X				X			X	X		SGRQ=St. George's Respiratory Questionnaire
PROMIS (fatigue items)			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PROMIS= Patient-reported outcomes measurement information system
SNOT-22			X								X							X	X		SNOT-22=Sino-nasal Outcomes Test-22 Questionnaire
Complete ADSD/ANSD		←========= daily =========→							X	X	X	X	X	X	X	X	X	X			ADSD/ANSD=Asthma Daily/Nightly Symptom Diary; To be completed daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Clinician-rated response to therapy							X				X				X			X	X		
Patient-rated response to therapy							X				X				X			X	X		
PGI-S		X	X				X		X		X				X			X	X		PGI-S: Patient Global Impression of Severity (of asthma)
PGI-C							X		X		X				X			X	X		PGI-C: Patient Global Impression of Change (from baseline of asthma severity)
Safety Assessments																					
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Ensure maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications are reviewed.
Physical Examination		X																X	X		Include height and weight for the complete physical exam at Screening Visit 1. Height can be omitted for subsequent visits.
Vital Signs		X	X			X			X		X	X			X		X	X	X		
12-lead ECG		X	X	X							X	X						X	X		ECG must be performed and assessed pre-dose. Twelve-lead ECG central over-read values should be used at all visits with the exception of Visit 2 and Visit 10 where 12-lead ECG machine read values should be used.
AE/SAE Assessment	X [g]	X [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE=Adverse events; SAE=Serious adverse events; see footnote g.

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Laboratory Assessments																					
Haematology with white blood cell count [f]		X [e]	X	X	X	X	X		X		X	X	X		X		X	X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing; see footnotes e and f.
Total IgE			X																		
Clinical Chemistry		X	X		X	X	X		X		X	X			X		X	X	X		Include liver chemistry.
Pregnancy Test (WOCBP only)		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	Serum pregnancy test should be done at screening Visit 1 and Exit Visit/Withdraw from study visit; urine pregnancy tests should be done for all other assessments; WOCBP=Women of childbearing potential; See Section 8.3.5 for additional information.
Urinalysis		X	(X)								X							X	X		Conduct at Visit 2 if not completed at Visit 1. Note: dipstick, send for analysis if abnormality is identified by dipstick
Anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			X																		ANA=antinuclear antibodies; MPO=myeloperoxidase; PR3=proteinase 3. Collected baseline sample will be stored and may be tested if necessary (see Section 7.5).
Complement C3 and C4			X				X				X				X			X	X		
PK sample			X	X	X	X	X		X		X	X	X		X			X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing.
Immunogenicity sample			X	X	X	X	X				X	X	X	X	X			X	X		

Protocol Activity	**Pre-Screening**	**Screening/Run-in**	**Intervention Period and Exit Visit (visit window is ±7 days)**																**Follow-up /Withdraw (±7 days)**		**Notes**
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Blood biomarker sample			X				X				X				X			X			Sample will be stored and may be analysed for exploratory biomarkers (see Section 8.7.3)
Genetics sample			←========== The genetics sample can be collected at Visit 2 or any visit after ==========→																		See footnote d.
Study intervention																					
Administer study intervention			X								X										Study intervention will only be administered in the clinic. Any scheduled assessments or sample draws should be performed beforehand. Monitor participant for at least 2h after administration (see Section 6.5).
eCRF/worksheets/other																					
Dispense Rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Register Visit in the IRT system		X	X								X								X		IRT=interactive response technology
Provide worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				The worksheet is a medical problems and healthcare utilisation worksheet.
Review worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
eDiary close out																		X	X		
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		eCRF=electronic Case Report Form

Protocol Activity	Pre-Screening	Screening/Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	**V0 [a]**	**Visit 1 [a]**	**V2[b] R***	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**Exit V17**	**WS[c]**	**FU**	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	**-8 to -6**	**-6 to -1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**26 or 52**	**56**	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	

a. Informed Consent must be obtained prior to initiating any study assessments. Pre-screening Visit 0 can occur any time from 0 to 14 days before Screening Visit 1.
b. Randomisation Visit 2 is 1 week after Screening Visit 1 but can be extended to up to 6 weeks after Visit 1 if, for example, a participant has an exacerbation during the run-in period. Results from Screening Visit 1 procedures must be available for review of randomisation criteria.
c. If a participant withdraws from the study, then the Withdraw from Study (WS) Visit should be conducted 26 weeks after the last administered dose of study intervention, i.e., at Week 26 if the second dose of study intervention was not received, or at Week 52 if the second dose of study intervention was received. A follow-up visit/call should also be conducted 30 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing.
d. Informed Consent for optional genetics research must be obtained before collecting a sample.
e. To be randomised, participants without a historical blood eosinophil count of ≥300 cells/µL in the 12 months prior to Screening Visit 1, must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. If the Screening Visit test result does not meet the blood eosinophil count eligibility criteria, the laboratory assessment may be repeated, at the discretion of the investigator, if it is judged to be likely in the eligible range for study inclusion within the run-in period prior to Visit 2.
f. For haematology samples collected after Randomisation, the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will not be reported to site staff and Sponsor (to maintain the treatment blind). However, sites will be sent total white blood counts throughout the study. Samples should be taken prior to dosing at Week 0 and Week 26 visits.
g. SAEs must be collected from signing of Informed Consent if considered related to study procedures.
h. If a patient fails the protocol-specified reversibility criterion or FEV_1 inclusion criteria, spirometry retest is allowed during the run-in period.

10.12. Appendix 12: Country-specific requirements

No country-specific requirements exist.

10.13. Appendix 13: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
ADE	Adverse device events
ADSD	Asthma Daily Symptom Diary
AE	Adverse event
ALT	Alanine transaminase
ANA	Antinuclear antibodies
ANCA	Anti-neutrophil cytoplasmic antibody
ANSD	Asthma Nightly Symptom Diary
Anti-HBc	Hepatitis B core antibody
Anti-IL-5	Anti-Interleukin-5
Anti-IL-5R	Anti-Interleukin-5 receptor
AST	Aspartate aminotransferase
BiPAP	Bilevel positive airway pressure
BP	Blood pressure
BUN	Blood urea nitrogen
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
cm	Centimetre
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CPAP	Continuous positive airway pressure
CPK	Creatine phosphokinase
CRF	Case report form
CS	Corticosteroid
CSR	Clinical study report
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Emergency department
eDiary	Electronic diary
EDTA	Ethylenediaminetetraacetic acid or disodium edetate
EGPA	Eosinophilic granulomatosis with polyangiitis
FAAN	Food Allergy and Anaphylaxis Network
FAS	Full Analysis Set
FEV_1	Forced expiratory volume in 1 second
FP	Fluticasone propionate
FSH	Follicle stimulating hormone
FTIH	First Time in Humans

FVC	Forced vital capacity
g	Grams
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	Gamma glutamyl transferase
GINA	Global Initiative for Asthma
GLDH	Glutamate dehydrogenase
GSK	GlaxoSmithKline
h	Hours
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HFA	Hydrofluoroalkane product
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IFU	Instruction for use
Ig	Immunoglobulin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IM	Intramuscular
IMP	Investigational medicinal product
INR	International normalised ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
kg	kilogram
L	Litre
LA	Long-acting
LABA	Long-acting β-agonist
LAM	Lactational amenorrhea method
LAMA	Long-acting muscarinic antagonist
LDH	Lactate dehydrogenase
LTRA	Leukotriene receptor antagonist
mAb	Monoclonal antibody
MAR	Missing at random

mcg (μg)	Microgram
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Millilitres
mm Hg	Millimetre of mercury
mol	Mole
MPO	myeloperoxidase
MSDS	Material Safety Data Sheet
msec	Milliseconds
NAb	Neutralising antibody
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NIMP	Non-investigational medicinal product
OCS	Oral corticosteroid
OLE	Open-label extension
PC_{20}	Provocative concentration causing a 20% fall in FEV_1
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PD_{20}	Provocative dose that decreases FEV_1 by 20%
PEF	Peak expiratory flow
PFS	Pre-filled safety syringe
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PR3	Proteinase 3
PRO	Patient-reported outcomes
PROMIS	Patient-reported outcomes measurement information system
QTcF	QTc corrected by Fridericia's formula
QTL	Quality tolerance limits
R&D	Research and Development
RBC	Red blood cell
RNA	Ribonucleic acid
SABA	Short-acting β-agonist
SADE	Serious adverse device event
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SDAC	Statistical data analysis centre
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SGRQ	St. George's Respiratory Questionnaire
SNOT	Sino-nasal Outcomes Test

SoA	Schedule of assessments
SoC	Standard of care
SOC	System organ class
SRM	Study Reference Manual
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
UACR	Urinary albumin-creatinine ratio
UK	United Kingdom
ULN	Upper Limit of Normal
w/v	Weight/volume
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential
µL	Microlitre

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10.14. Appendix 14: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

10.14.1. Amendment 1: 17-Aug-2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment: Amendment 01 is a global amendment to include modifications based on regulatory suggestion and additional changes were incorporated which align with program revisions and/or updates as listed in table below.

Section # and Name	Description of Change	Brief Rationale
Title page, Section 1.1 Synopsis and Section 2.1 Study Rationale	Addition of name “depemokimab”	To update the protocol with the recently approved generic name of GSK3511294
Section 1.3 Schedule of Activities and Table 6 of Appendix 11	Term “Demography and childbearing status” modified to “Demography data collection” Added text “Collection of exacerbations at Visit 1 is historical data” Term “Haematology with differential” modified to “Haematology with white blood cell count”. Added text to clarify that details regarding parasite screening are mentioned in study reference manual	Minor modification for more clarity
	Text “-56 to -7” modified to “-56 to -42”, “Week -8 to –1” modified to “Week -8 to -6”	Clarification
	Inclusion of an ECG at week 2 and week 28	Revision to address request of health authority
	Only screening, randomization, dispensing and withdrawal visits need interactive response technology (IRT), hence	Visits which require IRT registration were clarified

Section # and Name	Description of Change	Brief Rationale
	corrections made accordingly	
	Added Parasitic screening at week 48 Added a clinical chemistry visit at week 48	Modification with respect to the planned open label extension study
Section 1.1 Synopsis, Section 4.1 Overall design and Appendix 11	Added Visits 3 and 11 as in-person clinic visits.	Due to the inclusion of an ECG at week 2 and week 28 these visits can not be conducted remotely or virtually.
Section 4.1.1 Study Phases, Duration and Treatment Arms (Table 1)	Term “Clinic” modified to “Study”	Clarification
Section 5.1 Inclusion Criteria	Added text in inclusion criteria related to pregnancy	Clarification
Section 5.2 Exclusion Criteria	Exclusion of participants with allergy/intolerance to the excipients of GSK3511294 in Section 6.1	Updated wording for more clarity for study intervention and its excipients
Section 5.3.1 Randomization Inclusion Criteria	Airway reversibility or Airway hyperresponsiveness documented in the 24 months prior to Visit 2 instead of previous 12 months	To provide flexibility for enrolling participants that have demonstrated airway reversibility/hyperresponsiveness
Section 5.3.2 Randomization Exclusion Criteria	Revised QTc criteria	Revised wording for clarification
Section 6.9.1 Permitted Medications and Non-Drug Therapies	Text added for permission to receive COVID-19 Vaccine	Clarification considering the COVID-19 pandemic situation
Section 6.9.2 Prohibited Medications and Non-Drug Therapies	Removed “troleandomycin” from prohibited medication	As per the program level updated troleandomycin is no longer a prohibited medication
Section 6.9.3. Rescue Medicine	Low dose ICS/LABA is not permitted as rescue medication. Rescue medication usage will be recorded in the eDiary.	Revised wording for providing more clarity
Section 8.1.1 Pre-screening Visit (Visit 0)	Only screening (Visit 1), randomization (Visit 2), dispensing (Visit 10) and withdrawal visits need IRT, hence corrections made accordingly.	Visits which require IRT registration were clarified
Section 8.2.2 Asthma Exacerbations	Text deleted “Additional details on the process for determination	Text removed to align with the Statistical Analysis Plan

Section # and Name	Description of Change	Brief Rationale
	of clinically significant exacerbations can be found in the SAP".	
8.2.3.1. Reversibility using the Maximum Post-Bronchodilator Method	Current "The procedures involved in the Maximum Post-Bronchodilator Method are those generated by the **Pulmonary Physiology Subcommittee** " Previously "The procedures involved in the Maximum Post-Bronchodilator Method are those generated by the and not by *Asthma Clinical Research Network"* Current "Details of reversibility procedure mentioned in **SRM**" Previously "Details of reversibility procedure mentioned in in *third party vendor manual*"	Clarification
Section 8.2.4. St. George's Respiratory Questionnaire (SGRQ)	The SGRQ will contain 50 items instead of previous 51.	Clarification
Section 8.2.8. Patient Global Impression of Asthma Severity/Change (PGI-S, PGI-C), Section 8.2.10. Asthma Daily Symptom Diary/Asthma Nightly Symptom Diary (ADSD/ANSD)	Questionnaire only be administered to participants for whom an appropriate translation is available	Clarification
Section 8.2.10. Asthma Daily Symptom Diary/Asthma Nightly Symptom Diary (ADSD/ANSD)	Updated the information regarding use of ADSD and ANSD	Correction of the timeframe for completing daily symptom diary
Section 8.3.2 Vital Signs	Text "Oral or skin Temperature" modified to "Temperature"	Clarification
Section 8.6 Genetics and Pharmacogenomics, Section 8.7.3. Exploratory Biomarkers	Clarified that country specific requirements regarding genetic and biomarker samples will be mentioned in SRM	Country specific requirements will be specified in the SRM

Section # and Name	Description of Change	Brief Rationale
Section 9.3 Analysis sets	mITT description updated, Safety Population deleted	Revised description of mITT population to provide clarification that mITT population will be used as primary population for some other endpoints apart from efficacy.
	Clarification of analysis populations which will be defined in SAP.	Clarification
Appendix 2 Clinical Laboratory Tests	Added gamma glutamyl transferase to the table of protocol-required clinical laboratory test parameters.	Added to align with clinical laboratory worksheet.
Section 10.3.2 Definition of SAE	Modified definition of SAE	Revised as per the latest definition of SAE.
Section 10.3.5 Reporting of SAE to GSK	Removed the requirement of SAE reporting in eCRF within 72 hours	Removal of additional step of eCRF check.
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

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Summary of protocol changes (206713 and 213744)

Version 1.0 to 2.0	
Title page, Section 1.1 Synopsis and Section 2.1 Study Rationale	Addition of name "depemokimab"
Section 1.3 Schedule of Activities and Table 6 of Appendix 11	• Term "Demography and childbearing status" modified to "Demography data collection" • Added text "Collection of exacerbations at Visit 1 is historical data" • Term "Haematology with differential" modified to "Haematology with white blood cell count". • Added text to clarify that details regarding parasite screening are mentioned in study reference manual • Text "-56 to -7" modified to "-56 to -42", "Week -8 to –1" modified to "Week -8 to -6" • Inclusion of an ECG at week 2 and week 28 • Only screening, randomization, dispensing and withdrawal visits need interactive response technology (IRT), hence corrections made accordingly • Added Parasitic screening at week 48 • Added a clinical chemistry visit at week 48
Section 1.1 Synopsis, Section 4.1 Overall design and Appendix 11	Added Visits 3 and 11 as in-person clinic visits
Section 4.1.1 Study Phases, Duration and Treatment Arms (Table 1)	Term "Clinic" modified to "Study"
Section 5.1 Inclusion Criteria	Added text in inclusion criteria related to pregnancy
Section 5.2 Exclusion Criteria	Exclusion of participants with allergy/intolerance to the excipients of GSK3511294 in Section 6.1
Section 5.3.1 Randomization Inclusion Criteria	Airway reversibility or Airway hyperresponsiveness documented in the 24 months prior to Visit 2 instead of previous 12 months
Section 5.3.2 Randomization Exclusion Criteria	Revised QTc criteria
Section 6.9.1 Permitted Medications and Non-Drug Therapies	Text added for permission to receive COVID-19 Vaccine
Section 6.9.2 Prohibited Medications and Non-Drug Therapies	Removed "troleandomycin" from prohibited medication
Section 6.9.3. Rescue Medicine	Low dose ICS/LABA is not permitted as rescue medication. Rescue medication usage will be recorded in the eDiary.
Section 8.1.1 Prescreening Visit (Visit 0)	Only screening (Visit 1), randomization (Visit 2), dispensing (Visit 10) and withdrawal visits need IRT, hence corrections made accordingly.
Section 8.2.2 Asthma Exacerbations	Text deleted "Additional details on the process for determination of clinically significant exacerbations can be found in the SAP".
8.2.3.1. Reversibility using the Maximum Post-Bronchodilator Method	• Current "The procedures involved in the Maximum Post-Bronchodilator Method are those generated by the **Pulmonary Physiology Subcommittee**" Previously "The procedures involved in the Maximum Post-Bronchodilator Method are those generated by the and not by *Asthma Clinical Research Network*"

	• Current "Details of reversibility procedure mentioned in **SRM**" Previously "Details of reversibility procedure mentioned in in *third party vendor manual*"
Section 8.2.4. St. George's Respiratory Questionnaire (SGRQ)	The SGRQ will contain 50 items instead of previous 51.
Section 8.2.8. Patient Global Impression of Asthma Severity/Change (PGI-S, PGI-C), Section 8.2.10. Asthma Daily Symptom Diary/Asthma Nightly Symptom Diary (ADSD/ANSD)	Questionnaire only be administered to participants for whom an appropriate translation is available
Section 8.2.10. Asthma Daily Symptom Diary/Asthma Nightly Symptom Diary (ADSD/ANSD)	Updated the information regarding use of ADSD and ANSD
Section 8.3.2 Vital Signs	Text "Oral or skin Temperature" modified to "Temperature"
Section 8.6 Genetics and Pharmacogenomics, Section 8.7.3. Exploratory Biomarkers	Clarified that country specific requirements regarding genetic and biomarker samples will be mentioned in SRM
Section 9.3 Analysis Sets	• mITT description updated, Safety Population deleted • Clarification of analysis populations which will be defined in SAP
Appendix 2 Clinical Laboratory Tests	Added gamma glutamyl transferase to the table of protocol-required clinical laboratory test parameters.
Section 10.3.2 Definition of SAE	Modified definition of SAE
Section 10.3.5 Reporting of SAE to GSK	Removed the requirement of SAE reporting in eCRF within 72 hours
Throughout	Minor editorial and document formatting revisions
Version 2.0 to 3.0	
Section 1.3 Schedule of Activities (SoA)	• Added new footnote "h" spirometry retest allowed during the run in period if a patient fails the protocol-specified reversibility criterion or FEV1 inclusion criteria • Added text to clarify that pregnancy text should be done at screening Visit 1 and Exit Visit/Withdraw from study visit • Updated text in footnote "e" the Screening Visit laboratory assessment can be repeated during the run in period if a patient does not meet the blood eosinophil count eligibility criteria at the Screening Visit test result • Added text to clarify that, electrocardiogram (ECG) must be performed and assessed pre-dose • Added text to clarify that 12-lead ECG central over-read values should be used at all visits with the exception of Visit 2 and Visit 10 where 12-lead ECG machine read values should be used
Section 1.3 Schedule of Activities SoA (Urinalysis) 10.2 Appendix 2: Clinical Laboratory Tests Section 10.11 Appendix 11: Recommended measures Related to	(206713 only) Text added to clarify that for China sites the urine specimen may be sent to the central laboratory for routine urinalysis instead of performing a local urine dipstick. Urinalysis should be performed at Visit 1 so that results are available before randomisation at Visit 2 (206713 only)

COVID-19 Pandemic (Table 6)	
Section 2.3.1 Risk Assessment (QTc prolongation)	• Removed text related to postbaseline QTcF value of potential clinical importance from first time in human (FTIH) study (205722) • Updated text related to ECG parameters including corrected QT interval using Fridericia's formula (QTcF) for depemokimab treatment groups in the FTIH study (205722) • Updated wordings related to analysis of the relationship between depemokimab plasma concentrations and change from baseline QTcF data collected in FTIH 205722 study
Section 4.1 Overall Design Section 6.4.1 Treatment Assignment	Changed the ratio of medium/high ICS dose from 25% medium ICS dose and 75% high ICS dose to aiming up to 50% approximately of participants on medium ICS dose
Section 5.1 Inclusion Criteria	(206713 only) Added note to clarify that, in UK, Russia and Germany only adult participants (≥18 years) are to be included in this clinical trial
Section 5.2 Exclusion Criteria (Prior/Concomitant therapy)	Text added in exclusion criteria no. 12 to clarify that Authorized monoclonal antibodies (mAbs) treatments for COVID-19 are permitted
Section 5.2 Exclusion Criteria (Diagnostic Assesments)	Text added in exclusion criteria no.15 to clarify that the 12-lead ECG central over-read QTcF value is to be used
Section 5.3.2 Randomisation Exclusion Criteria	Text added in randomisation exclusion criteria no. 3 to clarify that the 12-lead ECG machine read QTcF value is to be used at Visit 2. The central over-read of the Screening Visit 1 12-lead ECG should be used to review ECG findings at Visit 2
Section 6.4.3 Controlled Early Access to Unblinded PK and PKPD Data	Added sub section and included text regarding controlled early access to Unblinded PK and PKPD Data to designated independent representative(s)
Section 6.9.1 Permitted Medications and Non-Drug Therapies	• "Additional asthma medications such as theophyllines and antileukotrienes will be permitted **as maintenance** provided that they have been taken regularly in the 3 months prior to screening (Visit 1)" • Removed repeated wordings about vaccination against SARSCoV-2 infection using authorized COVID-19 vaccines • Text added to clarify that participants can be treated for SARS-CoV-2 infection using authorized COVID-19 treatments (including mAbs) in line with local/national guidelines. Experimental COVID-19 treatments are not permitted
Section 7.1.2 QTc Stopping Criteria	• Text added to clarify that the QTcF value from the 12-lead ECG central over-read at randomisation Visit 2 should be used as baseline QTcF value for any changes from baseline calculations during the study • Text added to clarify that after randomisation 12-lead ECG central over-read values should be used to assess QTc stopping criteria, with the exception of Visit 10 (Week 26) where 12-lead ECG machine read values should be used
Section 8.1.2 Critical Assessment performed at Screening (Visit 1)	• Added new text to clarify that if the Screening Visit test result does not meet the blood eosinophil count eligibility criteria, the laboratory assessment may be repeated, at the discretion of the investigator • Added text for spirometry to clarify that if a patient fails the protocol-specified reversibility criterion or FEV1 inclusion criteria, spirometry restest is allowed during the run-in period
Section 8.3.3 Electrocardiograms (ECGs)	• Updated text related to additional ECGs to be performed if an ECG demonstrates a prolonged QTcF interval

Section 9.2.1 Sample Size Assumptions	(206713 only) Added text regarding the possibility that greater than 375 participants will be randomised in the study due to local country requests or requirements
Section 9.2.3 Sample Size Re-estimation or Adjustment	(206713 only) Text related to the data to be used for clinical study report has been deleted
Section 9.3 Analysis Sets	Updated text related to screened, enrolled, randomised, full analysis set, and safety population
Section 9.4.5 Safety Analyses	Safety population used for Safety analyses instead of mITT
Section 9.6 Interim Analysis	• Text deleted "no interim analyses are planned" • Added text that an unblinded interim analysis for futility will be performed • (206713 only) Added text to describe that blinded interim data will be used to complete a psychometric analysis of the ADSD/ANSD and PROMIS fatigue items
10.7.4 Recording and Follow-up of AE and/or SAE and Device Deficiencies (Assessment of Intensity)	Text deleted "other measures to evaluate AEs and SAEs may be utilised"
Appendix 10 Medium and High Daily Doses of Inhaled Corticosteroids	Footnote added to clarify GINA 2021 guidelines updates
Section 11 References	Added and updated the reference
Throughout	Minor editorial and document formatting revisions

Division	:	Worldwide Development
Information Type	:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Protocol Number: 206713

Compound Number: GSK3511294

Short Title: Placebo-controlled efficacy and safety study of GSK3511294 in participants with severe asthma with an eosinophilic phenotype

Acronym: SWIFT-1

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
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EudraCT	**2020-003612-28**

SAP Author(s):

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PPD , CPMS
PPD Patient Centred Outcomes, Value, Evidence and Outcomes

SAP Biostatistics Line Approval (Pharma TMF eSignature):

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VERSION HISTORY

Table 1 SAP Version History Summary

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1	20-Jan-2021	Version 01 Approval Date: 01-OCT-2020	Not Applicable	Original version

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 206173. Details of the planned final analyses are provided.

Descriptive study population analyses such as summary of demography and baseline characteristics and additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks
Other	
• To investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	• Time to first clinically significant exacerbation[a] • Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit • Change from baseline in SGRQ total score at discrete timepoints during the 52-week period

Objectives	Endpoints
	• Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period • SGRQ total score responder status at Week 52 (responder defined as achieving ≥4-point reduction from baseline) • ACQ-5 score responder status at Week 52 (responder defined as achieving ≥0.5-point reduction from baseline) • Change from baseline in Patient-Reported Outcomes Measurement Information Systems (PROMIS) Fatigue items score at discrete timepoints during the 52-week period • Change from baseline in Asthma Daily Symptom Diary (ADSD)/ Asthma Nightly Symptom Diary (ANSD) weekly mean score at specified timepoints during the 52-week period • Change from baseline in awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean • Change from baseline in morning peak expiratory flow (PEF) 2-week mean • Change from baseline in daily asthma symptom scores 2-week mean • Change from baseline in mean number of occasions of rescue medication use/day 2-week mean • Mean number of days with oral corticosteroids (OCS) usage over 52 weeks • Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period • Change from baseline in Sino-nasal Outcomes Test-22 (SNOT-22) score at discrete timepoints during the 52-week period
• To investigate GSK3511294 versus placebo on top of existing asthma therapy on	• Patient-rated response to therapy at discrete timepoints during the 52-week period

Objectives	Endpoints
• patient- and clinician-rated response to therapy • patient global impression of asthma severity and its change from baseline	• Clinician-rated response to therapy at discrete timepoints during the 52-week period • Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period • Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during the 52-week period
• To investigate the PD effects of GSK3511294	• Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period
• To investigate the PK of GSK3511294	• GSK3511294 plasma concentration at discrete timepoints during the 52-week period
Safety	
• To evaluate the safety and tolerability of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Incidence of AEs/SAEs • Laboratory parameters, including haematological and clinical chemistry parameters • Vital signs including blood pressure (BP), body temperature, and pulse rate • ECG assessments • Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294
Health Resource Use	
• To further evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on healthcare utilisation on top of existing asthma therapy	• Healthcare utilisation for asthma including hospitalisation, ED, and physician office/clinic visits

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit. For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

1.1.2. Estimands

Table 2 Estimands

The following two attributes apply to all estimands:

- Treatment comparison: GSK3511294 + SoC compared with placebo + SoC
- Population: Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Objectives	**Estimand**		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
Primary objective: To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	Annualised rate of clinically significant exacerbations over 52 weeks	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred	Ratio of the rates of exacerbations between GSK3511294 + SoC and placebo + SoC.

Objectives	**Estimand**		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		• Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring	
Secondary objective: to evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	a) Change from baseline in SGRQ total score at Week 52 b) Change from baseline in ACQ-5 score at Week 52 c) Change from baseline in pre-bronchodilator FEV_1 at Week 52	• Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be handled with a hypothetical strategy i.e. had the intercurrent event not occurred • Change in maintenance therapy or use of prohibited	a) Difference in mean change from baseline in SGRQ total score at Week 52 between GSK3511294 + SoC and placebo + SoC b) Difference in mean change from baseline in ACQ-5 score at Week 52 between GSK3511294 + SoC and placebo + SoC c) Difference in mean change from baseline in pre-bronchodilator FEV_1 at Week 52 between GSK3511294 + SoC and placebo + SoC

Objectives	**Estimand**		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	d) Annualised rate of clinically significant exacerbations requiring hospitalisation and/or ED visit over 52 weeks	medications (listed in protocol Section 6.9.2): to be handled with a treatment policy i.e. regardless of the intercurrent event occurring	d) Ratio of the rates of clinically significant exacerbations requiring hospitalisation and/or ED visit between GSK3511294 + SoC and placebo + SoC
Other objective: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	a) Time to first clinically significant exacerbation b) Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit c) Change from baseline in SGRQ total score at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred • Change in maintenance therapy or use of prohibited	a) Hazard ratio of first clinically significant exacerbation between GSK3511294 + SoC and placebo + SoC b) Hazard ratio of first clinically significant exacerbation requiring hospitalisation and/or ED visit between GSK3511294 + SoC and placebo + SoC c) Difference in mean change from baseline in SGRQ total score at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	d) Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period e) Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period f) Change from baseline in Sino-nasal Outcomes Test-22 (SNOT-22) score at discrete timepoints during the 52-week period g) Change from baseline in ADSD/ANSD weekly mean score at specified timepoints during the 52-week period	medications (listed in protocol Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring	d) Difference in mean change from baseline in ACQ-5 score at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC e) Difference in mean change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC f) Difference in mean change from baseline SNOT-22 score at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC g) Difference in mean change from baseline in ADSD/ ANSD

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
			weekly mean score between GSK3511294 + SoC and placebo + SoC
• **Other objective**: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	a) SGRQ total score responder status at Week 52 (responder defined as achieving ≥4-point reduction from baseline) b) ACQ-5 score responder status at Week 52 (responder defined as achieving ≥0.5-point reduction from baseline)	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred. Status following IE will be set as missing. • Change in maintenance therapy or use of prohibited	a) Odds ratio in SGRQ total score responder status at Week 52 between GSK3511294 + SoC and placebo + SoC b) Odds ratio in ACQ-5 score responder status at Week 52 between GSK3511294 + SoC and placebo + SoC

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		medications (listed in protocol Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring	
• **Other objective**: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	a) Change from baseline in PROMIS Fatigue items score at discrete timepoints during the 52-week period b) Change from baseline in awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean c) Change from baseline in morning peak expiratory flow (PEF) 2-week mean	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment.	a) Descriptive summary of change from baseline in PROMIS Fatigue items score by treatment group and by visit b) Descriptive summary of change from baseline in 2-weekly mean awakenings at night due to asthma symptoms requiring rescue medication use by treatment group and by time interval c) Descriptive summary of change from baseline in 2-week mean morning PEF by treatment group and by time interval

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	d) Change from baseline in daily asthma symptom scores 2-week mean e) Change from baseline in mean number of occasions of rescue medication use/day 2 week mean f) Mean number of days with oral corticosteroids (OCS) usage over 52 weeks	• Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data.	d) Descriptive summary of change from baseline in daily asthma symptom scores 2-week mean by treatment group and by time interval e) Descriptive summary of change from baseline in 2 week mean number of occasions of rescue medication use/day by treatment group and by visit and time interval f) Descriptive summary of mean number of days OCS usage over 52 weeks by treatment group
Other objective: to investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient- and clinician-rated response to therapy	a) Patient-rated response to therapy at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring. Summary will	Descriptive summary of (by treatment group) a) Patient-rated response to therapy at discrete timepoints during the 52-week period

Objectives	**Estimand**		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	b) Clinician-rated response to therapy at discrete timepoints during the 52-week period	include all on and off treatment data. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data.	b) Clinician-rated response to therapy at discrete timepoints during the 52-week period

Objectives	**Estimand**		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
Other objective: to investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient global impression of asthma severity and its change from baseline	a) Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period b) Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred • Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring	Odds ratio in a) PGI-S of asthma at discrete timepoints during the 52-week period b) PGI-C from baseline of asthma severity at discrete timepoints during the 52-week period

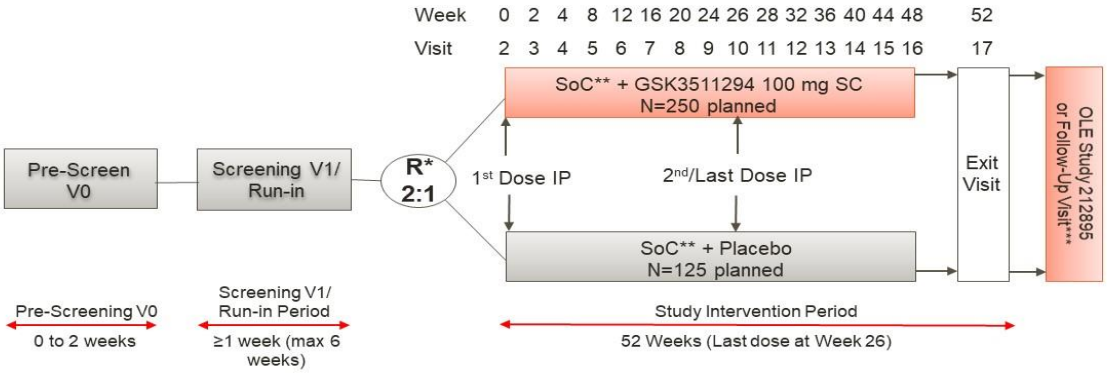
Objectives	**Estimand**		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
Other objective: to investigate the PD effects of GSK3511294	Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: while on treatment strategy i.e. only data collected while participant was on-treatment will be used on the analysis. Blood eosinophil counts taken more than 26 weeks following last dose will not be included in the analysis. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: same as above • Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2):hypothetical strategy, i.e.had the	ratio in absolute blood eosinophil count GSK3511294 + SoC vs. placebo + SoC

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		intercurrent event not occurred. •	
Other objective: to investigate the PK of GSK3511294	GSK3511294 plasma concentration at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Change in maintenance therapy or use of prohibited	Descriptive summarise of GSK3511294 plasma concentration by visit. (GSK3511294 + SoC arm only)

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		medications (listed in protocol Section 6.9.2): hypothetical strategy, i.e.had the intercurrent event not occurred.	
Safety objective: To evaluate the safety and tolerability of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	a) Incidence of AEs/SAEs b) Laboratory parameters, including haematological and clinical chemistry parameters c) Vital signs including blood pressure (BP), body temperature, and pulse rate d) ECG assessments e) Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually	Descriptive summaries of a) Incidence of AEs/SAEs b) Laboratory parameters, including haematological and clinical chemistry parameters c) Vital signs including blood pressure (BP), body temperature, and pulse rate d) ECG assessments e) Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294

Objectives	**Estimand**		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		received their randomised treatment. • Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring	
Health Resource Use: To further evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on healthcare utilisation on top of existing asthma therapy	Healthcare utilisation for asthma including hospitalisation (including ICU admissions and Length of Stay-LOS), ED, and physician office/clinic visits (scheduled and unscheduled)	Same strategy as per primary endpoint	Descriptive summarise of healthcare utilisation

1.2. Study Design

Overview of Study Design and Key Features
 ** R = Randomisation: To be randomised participants without a historical blood eosinophil count of ≥300 cells/µL must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. Participants will remain on their standard of care (SoC) asthma therapy throughout the intervention period and will be randomised 2:1 to receive GSK3511294 (100 mg) or placebo.* *** SoC = medium to high dose ICS (≥440 µg FP HFA daily or clinical comparability) plus additional controller. SoC asthma therapy to exclude biologics.* **** OLE = Open label extension. Willing participants will continue directly into OLE Study 212895. Participants unwilling to continue will have a follow-up visit 4 weeks after the Exit Visit.*

Design Features	• Phase 3A • 52-week treatment period • Randomised • Double-blind • Placebo-controlled • Parallel group • Multi-centre • Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125). • A sample size of 375 randomised will provide 99% power to demonstrate superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC in annualised rate of clinically significant exacerbations over 52 weeks, based on the true annualised rate of exacerbations in the placebo arm being 1.18 , an assumed true treatment difference of a 50% reduction and at a 5% two-sided significance level. • Participants who receive both doses of study intervention and complete the Exit Visit will be eligible to participate in an open-label extension (OLE) study (Study 212895), during which they will receive two doses of open-label GSK3511294 100 mg SC over another 52 weeks.
Study intervention and Study intervention Assignment	The study will consist of a pre-screen period (0-2 weeks), a run-in period (1-6 weeks), and a study intervention period (52 weeks). After the run-in period, participants will be randomised in a 2:1 ratio using an interactive response technology (IRT) system in a blinded manner to receive either GSK3511294 100 mg or placebo by SC injection. Randomisation will be stratified based on baseline ICS dose (medium or high dose). Two doses of study intervention will be administered in the clinic: the first at randomisation Visit 2 (Week 0) and the

Overview of Study Design and Key Features	
	second at Visit 10 (Week 26). Participants will be assessed at each scheduled visit (a total of 17 study visits) during the 52-week treatment phase. Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 10, Exit Visit 17, and WS Visit (if applicable). Participants will remain on their existing stable maintenance asthma therapy throughout the study.
Interim Analysis	• No interim analyses of efficacy data are planned. • IDMC review of safety data is planned.

2. STATISTICAL HYPOTHESES

The primary study objective is to test for the superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC, assessed by the annualised rate of clinically significant exacerbations measured over the study intervention period of 52 weeks.

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 and placebo.

2.1. Multiplicity Adjustment

The treatment comparison of interest for the primary and secondary endpoints is GSK3511294 100 mg SC + SoC vs placebo + SoC. A fixed sequence hierarchical testing procedure will be used to provide strong control of Type I error for multiplicity arising from the primary and multiple secondary endpoints. This will be carried out using a stepdown closed testing procedure where inference for an endpoint in the predefined hierarchy will be dependent on statistical significance having been achieved for the previous endpoints in the hierarchy. For example, for the primary endpoint, GSK3511294 + SoC will be compared to placebo + SoC at a two-sided 5% level. The next endpoint in the hierarchy (i.e. the first secondary endpoint) will be tested only if the test for the primary endpoint is significant at the two-sided 5% level. Testing will continue down the hierarchy for the remaining endpoints in an equivalent manner only if the previous endpoint in the hierarchy achieves statistical significance.

The hierarchy of the primary and secondary endpoints to be tested is as follows:

1. Annualised rate of clinically significant exacerbations over 52 weeks
2. Change from baseline in SGRQ at Week 52
3. Change from baseline in ACQ-5 at Week 52
4. Change from baseline in clinic pre-bronchodilator FEV_1 at Week 52
5. Annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled	All participants who sign the ICF and for whom a record exists.	Study Population
Modified Intent-to-Treat (mITT)	All randomised participants who receive at least one dose of study intervention. This population will serve as the primary population for analyses of study population, efficacy, safety, immunogenicity, PD and health resource use endpoints. Data will be analysed according to randomised treatment arm.	• Study Population • Efficacy • Safety • Immunogenicity • PD • Health Resource Use
mITT-PROMIS	All participants in the mITT population for whom at least one PROMIS fatigue items were administered	• Efficacy (PROMIS)
mITT-SNOT-22	All participants in the mITT population for whom at least one SNOT-22 questionnaire were administered	• Efficacy (SNOT-22)
PK	All participants in the mITT population for whom at least one pharmacokinetic sample was obtained, analysed and was measurable.	• PK

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The Modified Intent-to-Treat (mITT) Analysis Set will be used for all Study Population, Efficacy, Safety, Immunogenicity and PD analyses, unless otherwise stated. The Output and Programming Specification (OPS) document will provide more details.

Confidence intervals will use 95% confidence intervals (CI) unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum.

Categorical data will be summarized as the number and percentage of participants in each category.

For endpoints that are formally modelled, summary statistics will be provided.

Where statistical models are used, if there are important departures from the distributional assumptions, transformations of covariates or alternative models may be explored as supporting analyses.

Randomisation is stratified based on baseline ICS dose (medium or high). All statistical models will include this stratum as a covariate. In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the data collected in the CRF, not the assigned stratum at randomization.

Assessments collected at withdrawal visit will be included in summary tables but won't be included in any statistical analysis.

4.1.2. Baseline Definition

Baseline values for visit based assessments and eDiary assessments are defined in Table 3.

In general, the baseline values for visit based assessment will be the Visit 2 pre-dose assessment. If a value is missing at visit 2 then the value recorded at visit 1 (screening) will be used as the baseline.

Unless otherwise stated, if baseline is missing no derivation will be performed and baseline will be set to missing.

Table 3 Baseline Definitions & Derivations

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
Efficacy, Health Outcomes and Other			
SGRQ total and domain scores		X	Day 1 pre-dose
ACQ-5		X	Day 1 pre-dose
Pre-bronchodilator FEV_1	X	X	Day 1 pre-dose
Post-bronchodilator FEV_1	X	X	Day 1 pre-dose
PROMIS Fatigue items score		X	Day 1 pre-dose

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
ADSD/ANSD weekly mean score	X (daily following Screening)		Average of measurements from Day -7 to Day 1 inclusive (at least 4 days must be non-missing)
awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean	X (daily following Screening)		Average of measurements from Day -7 to Day 1 inclusive (at least 4 days must be non-missing)
morning PEF 2-week mean	X (daily following Screening)		Average of measurements from Day -7 to Day 1 inclusive (at least 4 days must be non-missing)
daily asthma symptom scores 2-week mean	X (daily following Screening)		Average of measurements from Day -7 to Day 1 inclusive (at least 4 days must be non-missing)
mean number of occasions of rescue medication use/day 2-week mean	X (daily following Screening)		Average of measurements from Day -7 to Day 1 inclusive (at least 4 days must be non-missing)
SNOT-22 score		X	Day 1 pre-dose
PGI-S	X	X	Day 1 pre-dose
Safety			
Blood pressure	X	X	Values from most recent assessment prior to first dose of study treatment which records both systolic and diastolic BP
Pulse rate	X	X	Most recent individual value prior to first dose of study treatment
Clinical Chemistry	X	X	Most recent individual value prior to first dose of study treatment
ECG endpoints	X	X	Values from most recent ECG conducted prior to first dose of study treatment
Hematology with differential (including eosinophil count)	X	X	Most recent individual value prior to first dose of study treatment

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
Other			
Complement C3 and C4		X	Day 1 pre-dose
Immunogenicity		X	Day 1 pre-dose

NOTES :

- Only records that have been assigned a treatment phase of 'pre-treatment' will be considered as baseline assessments.
- Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

4.1.3. Multicenter Studies

For the purposes of covariate adjustment in the statistical analysis, countries will be grouped into regions. The following regions are defined:

- European (Czechia, France, Germany, Italy, Poland, Spain, UK)
- US
- Rest of World (Canada, China, Russia)

If there are insufficient subjects in each region for the statistical procedures to converge satisfactorily, the combining of regions will be considered.

4.2. Primary Endpoint Analyses

4.2.1. Definition of endpoint

The primary endpoint is the annualized rate of clinically significant exacerbations over the 52 weeks following randomisation.

Clinically significant exacerbations of asthma are defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see protocol Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

Exacerbations recorded in the eCRF are considered as verified clinically significant exacerbations and will be included in the primary analysis.

Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

4.2.2. Main analytical approach

Primary Statistical Analyses
Endpoint(s)
• Annualized rate of clinically significant exacerbations over 52 weeks
Model Specification

• Generalized linear model assuming a negative binomial distribution
• Terms in the model:
  • **Response**: number of recorded clinically significant exacerbations experienced per subject.
  • **Categorical**: treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbation history (as an ordinal variable (2, 3, 4+)), baseline ICS dose (medium, high), geographical region
  • **Continuous**: baseline pre-bronchodilator % predicted FEV_1
  • **Offset**: Log_e(total time in the study in years)

Model Checking & Diagnostics
• The fit of the regression models will be examined using "Q-Q" plots of the standardized residuals. Interpretation of these plots will be aided by the addition of simulation-generated tolerance boundaries.
Results Presentation
• Treatment group model estimated annualized exacerbation rates and associated 95% CI • pairwise treatment rate ratios and associated p-value and 95% CI. • pairwise treatment percent reductions in annual exacerbation rate and associated 95% CI
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed "missing at random" (MAR) (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the primary endpoint, the data for the period following withdrawal will be assumed MAR (based on all data included in the analysis under the current estimand strategy).
Subgroup Analysis
• By baseline ICS dose (medium, high) subgroup analysis will be performed.

4.2.3. Sensitivity analyses

For the main analytical approach, data that is missing due to study withdrawal is assumed to be missing at random. The aim of sensitivity analyses is to assess the robustness in the treatment effect and conclusion in the main analytical approach when departing from the missing at random assumption. Two sensitivity analyses will be performed to for this investigation.

4.2.3.1. Sensitivity Analysis 1 (MNAR Based on off-treatment Data)

This sensitivity analysis will be performed where subjects who withdrew from the study early will have missing data imputed for the period of time between withdrawal from the

study to the Week 52 visit based on the off-treatment data collected from subjects who continued in the study following discontinuation of randomised intervention. Multiple imputation methods will be used with results combined across imputations using Rubin's method [Roger, 2018].

If the total unobserved/excluded time in the study is <3% of the total study duration or if <50% of the total off-treatment period is observed then the sensitivity analysis will not be conducted.

4.2.3.2. Sensitivity Analysis 2 (Tipping Point Analysis)

Tipping point analysis will explore the impact of missing data by using differing assumptions regarding the exacerbation rate in subjects who withdraw from the study. Subjects who withdrew from study early will have missing data imputed for the period of time between withdrawal from the study to the Week 52 visit based on a range of values for the rate of exacerbations per year following study withdrawal. The values to be investigated will be based on increases relative to the estimated rates obtained within each arm under the MAR assumption. The imputed exacerbation rates will vary independently for the active and placebo arms, and will include scenarios where subjects in the active arm have worse outcomes following early withdrawal from the study than subjects in the placebo arm. The tipping point multiple imputation method will be based on pattern mixture models [Keene, 2014]. The results from the analyses of each sample are combined using Rubin's method.

If the total unobserved/excluded time in the study is <3% of the total study duration or if <50% of the total off-treatment period is observed then the sensitivity analysis will not be conducted.

4.3. Secondary Endpoints Analyses

4.3.1. Definition of endpoint(s)

The secondary endpoints are:

- Change from baseline in SGRQ total score at Week 52
- Change from baseline in ACQ-5 score at Week 52
- Change from baseline in pre-bronchodilator FEV_1 at Week 52
- Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks

4.3.2. Main analytical approach for SGRQ total score, ACQ-5 score and pre-bronchodilator FEV_1

Secondary Endpoints Analyses
Endpoint(s)
• Change from baseline in SGRQ total score at Week 52 • Change from baseline in ACQ-5 score at Week 52 • Change from baseline in pre-bronchodilator FEV_1 at Week 52

Secondary Endpoints Analyses

Model Specification

- Mixed Models Repeated Measures (MMRM) model.
- Terms in the model:
  Response: SGRQ Total score or ACQ-5 score or pre-bronchodilator FEV1 at each visit.
  Categorical: treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high), exacerbation history (as an ordinal variable (2, 3, 4+)), geographical region, visit
  Continuous: baseline (SGRQ Total score, or ACQ-5 score, baseline pre-bronchodilator % predicted FEV1
  Interaction: baseline*visit, treatment group*visit
  Repeated: visit
- The MMRM analysis for SGRQ total scores will include data collected at Weeks 4, 12, 26, 40 and 52.
  The MMRM analysis for ACQ-5 score will include data collected at Weeks 2, 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48 and 52.
  The MMRM analysis for pre-bronchodilator FEV1 will include data collected at Weeks 26 and 52.
- The model will be fit with an unstructured variance-covariance matrix.
- The Kenward and Roger method (KR) for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. In the event the model fails to run using the KR method, then the residual method will be used instead. In the event the model fails to run using residual method and assessments are from many timepoints, timepoints included in the analysis may be reduced by keeping the timepoints/intervals of most interest.
- Baseline is defined in Section 4.1.2
- Two models will be fitted; one with a response variable of change from baseline and one with the response variable as the raw value.

Model Checking & Diagnostics

- The fit of the regression models will be examined using “Q-Q” plots of the standardized residuals. Interpretation of these plots will be aided by the addition of simulation-generated tolerance boundaries.

Results Presentation

- Least-square (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI and P-values for each visit will be presented.
- The LS mean treatment differences (and associated 95% CIs) for all visits will also be presented graphically.
- SGRQ total scores, ACQ-5 score and pre-bronchodilator FEV1 (absolute value and changes from baseline) will also be summarised by treatment group and visit.

Handling of missing data and data excluded due to intercurrent events

- For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy).
- For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.3.3. Main analytical approach for annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

The annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks will be analysed using a negative binomial generalised linear model, as described for the primary endpoint, Section 4.2.2 for details.

4.3.4. Sensitivity analyses

The sensitivity analyses for the primary endpoint as described in Section 4.2.3 will also be performed for the secondary endpoints.

4.4. Other Endpoints Analyses

4.4.1. Time to first clinically significant exacerbation and Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit

Other Endpoints Analyses
Endpoint(s)
• Time to first clinically significant exacerbation • Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit
Model Specification
• Cox's proportional hazards model • Terms in the model: **Response**: time to first clinically significant exacerbation or first clinically significant exacerbation requiring hospitalization and/or ED visit **Categorical**: treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbation history (as an ordinal variable (2, 3, 4+)), baseline ICS dose (medium, high), geographical region **Continuous**: baseline pre-bronchodilator % predicted FEV1 • The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead. • Kaplan-Meier survivor functions will be obtained for each treatment group using PROC LIFETEST with a TIME statement.
Model Checking & Diagnostics
• The proportional hazards assumption will be examined by obtaining the Kaplan-Meier estimates of the survival function S(t) over time separately for each treatment group. In addition, the ln {-ln[S(t)]} plot will be produced.
Results Presentation
• Hazard ratios and the percent reduction in risk for the pairwise treatment comparisons with associated 95% CIs and p-values will be presented. • The Kaplan-Meier curves will be presented showing the probability of having an event over time for each treatment group separately plotted on the same figure.
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis.

Other Endpoints Analyses
Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.2. Change from baseline in SGRQ total score and in ACQ-5 score at discrete timepoints during the 52-week period

Analytic approach for change from baseline in SGRQ total score and change from baseline in ACQ-5 score at discrete timepoints during the 52-week period has been included in the secondary endpoints analyse, see Section 4.3.2 for details.

4.4.3. SGRQ total score responder status at Week 52 and ACQ-5 score responder status at Week 52

Other Endpoints Analyses
Endpoint(s)
• Proportion of responders according to SGRQ total score (responder defined as achieving ≥4-point reduction from baseline) • Proportion of responders according to ACQ-5 score (responder defined as achieving ≥0.5-point reduction from baseline)
Model Specification
Generalized linear mixed model • Terms in the model: **Dependent:** response (yes/no) **Categorical:** treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high), exacerbation history (as an ordinal variable (2, 3, 4+)), geographical region, visit, subject **Continuous**: baseline (SGRQ Total score, or ACQ-5 score), baseline pre-bronchodilator % predicted FEV1 **Interaction:** baseline (SGRQ Total score, or ACQ-5 score)*visit, treatment group*visit The model will be fit with an unstructured variance-covariance matrix with one single model to include all visits where the assessment in question is scheduled to be performed. • Computation of confidence intervals for the odds ratios is based on the individual Wald tests. • The analysis of responder based on SGRQ total scores will include data collected at Weeks 4, 12, 26, 40 and 52. The analysis of responder based on ACQ-5 score will include data collected at Weeks 2, 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48 and 52. • In the event the model fails to run and assessments are from many timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest.

Model Checking & Diagnostics
• Pearson residuals will be plotted by using PLOTS=PEARSONPANEL option for the model statement in SAS.
Results Presentation
• Number and percentage of responders and non-responders for each treatment at each visit • Odds ratio for pairwise comparisons with associated 95 % CIs and p-values
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.4. Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1

Analytic approach for change from baseline in pre-bronchodilator FEV_1 at discrete timepoints during the 52-week period has been included in the secondary endpoint analysis of change from baseline in pre-bronchodilator FEV_1 at Week 52, see Section 4.3.2 for details.

Change from baseline in post-bronchodilator FEV_1 at discrete timepoints during the 52-week period will be analyzed in the same approach as for change from baseline in pre-bronchodilator FEV_1.

4.4.5. PROMIS Fatigue items score

PROMIS Fatigue items score and change from baseline in PROMIS Fatigue items score will be summaried by treatment group and visit.

4.4.6. SNOT-22 score

The SNOT-22 questionnaire is administered (post randomisation) at Week 26 and 52. The 22 questions of the SNOT-22 are each graded on a 6-point scale ranging from 0 = 'no symptoms' to 5 = 'as bad as things could be'. The scores for each of the questions are summed to derive the total score which ranges from 0 to 110, with higher scores representing worse quality of life.

Other Endpoints Analyses
Endpoint(s)
• Change from baseline in SNOT-22 total score at Week 26 and Week 52
Model Specification, Model Checking & Diagnostics
• See Model Specification, Model Checking & Diagnostics for secondary endpoints statistical analyses • analysis will include data collected at Weeks 26 and 52.

Model Results Presentation
• See Model Results Presentation for secondary endpoints statistical analyses (figures will not be presented) • SNOT-22 score (absolute value and changes from baseline) will also be summarised by treatment group and visit.
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.7. Patient-rated response to therapy during the 52-week period

This is an overall evaluation of response to treatment, conducted by the participant at Week 12, 26, 40 and 52 using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse

Patients rated response to therapy will be summarised by treatment group and visit.

4.4.8. Clinician-rated response to therapy during the 52-week period

This is an overall evaluation of response to treatment, conducted by the investigator at Week 12, 26, 40 and 52 using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse

Clinician rated response to therapy will be summarised by treatment group and visit.

4.4.9. Patient Global Impression of Asthma Severity/Change (PGI-S, PGI-C)

Patient Global Impression of Asthma Severity (PGI-S): The participant will complete a PGI-S question at the visits: Randomisation and Screening, Day 1, Week 12, 20, 26, 40, 52. This single global question will ask participants to rate their asthma severity on a five-point scale (no symptoms, mild, moderate, severe, very severe). Responses will be captured electronically.

Patient Global Impression of Change (PGI-C) from Baseline of Asthma Severity: The participant will complete a PGI-C question from baseline of their asthma severity at Week 12, 20, 26, 40 and 52. The single question will ask participants to rate the overall change in their asthma severity compared with Day 1 (randomisation) prior to start of study intervention. The rating will use a five-point scale (much better, a little better, no change, a little worse, much worse) and responses will be captured electronically.

Other Endpoints Analyses
Endpoint(s)
• Patient global impression of asthma severity (PGI-S) • Patient global impression of change (PGI-C) from baseline of asthma severity
Model Specification
• Ordinal Logistic regression model (proportional odds model) • Terms in the model: Dependent: response (5-point scale) Categorical: treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high), exacerbation history (as an ordinal variable (2, 3, 4+)), geographical region Continuous: baseline pre-bronchodilator % predicted FEV1 • The model will be fit at each visit (Weeks 12, 20, 26, 40 and 52). • Subjects with a missing response at a particular visit will be included in the "Significantly Worse" category in the ordinal logistic regression model for the analysis of that visit. • Inference will primarily be based on the Week 24 comparison.
Model Checking & Diagnostics
• The proportional hazards assumption will be examined by obtaining the Kaplan-Meier estimates of the survival function S(t) over time separately for each treatment group. In addition, the ln {-ln[S(t)]} plot will be produced.
Results Presentation
• The number and percentage of subjects in each response category and with a missing response summarised by treatment group for each visit. • The estimated odds ratio for the treatment variable in the ordinal logistic regression model and corresponding 95% CI and p-value
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy).

Other Endpoints Analyses
• For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.10. ADSD/ANSD (and responder based on ADSD/ANSD)

The ADSD/ANSD is a 6-item self-administered patient-reported diary developed by the PRO Consortium's Asthma Working Group (in accordance with the Food and Drug Administration's PRO Guidance) to facilitate comprehensive and reliable assessment of asthma symptoms from a patient's perspective which received qualification from the FDA in March 2019 supporting use in drug development as an exploratory measure.

The ADSD/ANSD is intended for use by adults and adolescents (aged 12 years and older) who are diagnosed with asthma to rate the severity of their symptoms in the three core categories: breathing symptoms (wheezing, shortness of breath), chest symptoms (chest tightness, chest pain) and cough.

The ADSD/ANSD must be completed twice daily by the participant daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.:

- The morning diary (ADSD) is to be completed upon waking and refers to asthma symptoms during the night-time.
- The evening diary (ANSD) is to be completed before going to bed and refers to asthma symptoms during the day.

Participants are required to rate the six symptoms at their worst during the respective timeframes using an 11-point numeric rating scale (NRS) ranging from 0 ('None') to 10 ('As bad as you can imagine'). Responses will be captured electronically.

To date no definition of meaningful within-patient change has been published. GSK studies 214135 and 214566 will complete prior to LSLV in this study and will provide this definition of response required to interpret change from baseline and to be used in responder analysis. Therefore, details of responder analysis will be subject to a SAP amendment (or a supplementary SAP) at a later stage.

Other Endpoints Analyses
Endpoint(s)
• Change from baseline in Asthma Daily Symptom Diary (ADSD) weekly mean score at timepoints during the 52-week period (weekly up to Week 16 and then every visit) • Change from baseline in Asthma Nightly Symptom Diary (ANSD) weekly mean score at timepoints during the 52-week period (weekly up to Week 16 and then every visit)
Model Specification, Model Checking & Diagnostics
• Similar to model specification, model checking and diagnostics detailed in Section 4.3.2 • Response variable: weekly mean scores • Baseline score is defined in Section 4.1.2

Model Results Presentation
• LS means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI and P-values for each Week will be presented. • The LS mean treatment differences (and associated 95% CIs) for all weeks will also be presented graphically. • ADSD and ANSD weekly mean absolute score and changes from baseline will also be summarised by treatment group and visit. Summary will include weekly mean score at all visits (including all weeks prior to week 16). .
Handling of missing data and data excluded due to intercurrent events
• Same approach as described in Section 4.3.2

4.4.11. Mean number of occasions of rescue medication per day

Daily diary data for rescue medication (salbutamol/albuterol) use will be aggregated over 2-week periods, then the mean daily usage, excluding days with missing data, will be calculated for each 2-week period (Weeks 1-2, 3-4,…, 51-52). Data for each 2-week period, and change from baseline for each 2-week period will be summarised by treatment group and visit. For definition of baseline see Section 4.1.2.

4.4.12. Awakenings at night due to asthma symptoms requiring rescue medication use

Awakening at night due to asthma symptoms requiring rescue medication use will be summarised as for rescue medication use, see Section 4.4.11.

4.4.13. Morning peak expiratory flow (PEF)

Morning PEF will be summarised as for rescue medication use, see Section 4.4.11.

The summaries will be for :

1) all data included as per mITT population
2) excluding data where asthma medication was taken up to 6 hours prior to PEF assessment

4.4.14. Daily asthma symptom scores

Daily asthma symptom score will be summarised as for rescue medication use, see Section 4.4.11.

4.4.15. Number of days with oral corticosteroids

Total number of days of oral corticosteroids (OCS) use over 52 weeks that are associated with clinically significant exacerbations per subject will be summarised by treatment group. Also, number of clinically significant exacerbations, number of clinically significant exacerbations treated with OCS, and mean number of days using OCS per

clinically significant exacerbations treated with OCS will be summarised by treatment group.

Number of subjects on maintenance OCS at screening, total number of days of maintenance OCS use over 52 weeks and mean number of days of maintenance OCS use per subject will also be summarised by treatment group.

4.5. CLINICAL PHARMACOLOGY DATA ANALYSES

4.5.1. Pharmacokinetic Analyses

In this study, GSK3511294 plasma concentration are collected at discrete timepoints during the 52-week treatment period. GSK3511294 plasma concentration will be summarised by visit. (GSK3511294 + SoC arm only).

The PK data from this study will be included in a meta-analysis of the PK and PKPD data across all GSK3511294 studies. Details of meta-analysis will be in a separate CPMS RAP.

4.5.2. Pharmacodynamic Analyses - Blood Eosinophils

Blood eosinophil counts will be loge-transformed prior to analysis. Non-detectable blood eosinophil values of 0 GI/L, or results below the limit of quantification will be imputed by half of the lowest observed detectable (non-zero) value in the study dataset, prior to log transformation.

Ratio to baseline during W52 will be analysed using a MMRM analysis. Model specification, model checking and diagnostics are the same as described for secondary endpoints statistical analyses, see Section 4.3.1. Analysis will include data from all visits that blood eosinophils data is collected. LS Mean (SE) and LS Mean ratio to screening (SE) in each treatment group will be presented. Mean treatment ratio and 95% CI for GSK3511294 vs placebo will also be presented.

Absolute and ratio to baseline blood eosinophil counts will be summarised by treatment group and visit. Only results from the central laboratory will be included in the summary, however all data will be listed.

4.6. Safety Analyses

All safety analyses will be performed on the mITT Analysis Set. Data will be analysed according to randomised treatment arm except for the very unlikely case that participant has taken all treatments differed to randomised treatment. In this case, the actual treatment for this participant will be used in the analysis. Summaries of data will report data according to the nominal visit for which it was recorded. Occurrence of Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESIs), laboratory data, vital signs, and ECGs will be included in data displays in the form of listings, frequency tables, summary statistics, graphs, and statistical analyses

where appropriate. In addition, a listing of AEs will be produced for all participants who received at least once other than randomised treatment during the study

4.6.1. Extent of Exposure

Two doses of study treatment will be administered during study treatment period: the first at randomisation Visit 2 (Week 0) and the second at Visit 10 (Week 26). Each dose is viewed as providing therapeutic coverage for 26 weeks (182 days). The number of treatments administered and the number of days exposure will be summarised descriptively and listed. Total subject-year exposure will also be presented.

Number of days of exposure to study treatment will be calculated as follow:
Duration of Exposure in Days = (Date of Final Dose) – (Date of First Dose) + 182

Subject years exposure is calculated as follow:

Subject Years Exposure = ((Date of Final Dose) – (Date of First Dose) + 182)/365.25

The exposure summary will also be presented by age subgroup (12-17, 18-64, ≥65).

4.6.2. Adverse Events

Adverse events analyses including the analysis of adverse events (AEs), Serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards.

An overview summary of AEs, including counts and percentages of participants with any AE, AEs related to study intervention, AEs leading to permanent discontinuation of study intervention or withdrawal from study, study intervention related AEs leading to permanent discontinuation of study intervention or withdrawal from study, SAEs, SAEs related to study intervention, fatal SAEs, and fatal SAEs related to study intervention will be produced. These summaries will also be produced by age subgroup (12-17, 18-64, ≥65).

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

The frequency and percentage of AEs will be summarized in two ways: 1) in descending order by System Organ Class (SOC) and Preferred Term (PT). 2) in descending order by PT only.

A separate summary will be provided for study intervention-related AEs. A study intervention-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as “Yes”. A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study intervention as ‘Yes’ or missing. The summary table will be displayed in descending order by SOC and PT.

All SAEs will be tabulated based on the number and percentage of participants who experienced the event. Separate summaries will also be provided for study intervention-related SAEs. The summary tables will be displayed in descending order by SOC and PT.

A study intervention-related SAE is defined as an SAE for which the investigator classifies the relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study intervention as 'Yes' or missing. The summary table will be displayed in descending order by SOC and PT.

4.6.2.1. Adverse Events of Special Interest

Adverse events of special interest (AESI) for GSK3511294 program include:

- Allergic reactions including anaphylaxis

  Note: these events will be assessed by the investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis.

- Type III hypersensitivity (immune complex disease/vasculitis) reactions
- Local injection site reactions
- QTc prolongation

AESI reported by the investigator as systemic reactions (further categorised by the investigator as either allergic [type I hypersensitivity] or other systemic reactions and assessed against Sampson criteria for anaphylaxis) are collected via targeted eCRF within the study. Vasculitis events and local injection site reactions are also collected via targeted eCRF within the study.

Separate summary tables showing the number and percent of subjects with each type of AESI (excluding QTc prolongation) broken down by preferred term will be created.

For each type of AESI (excluding QTc prolongation) a profile summary table will be produced containing information including, but not limited to, the number of occurrences of the event, event characteristics, time to onset, intensity, outcome and action taken.

A summary of the incidence of serious adverse events and adverse events of special interest (excluding QTc prolongation) will be produced displaying the relative risk and risk difference and their 95% CIs between and GSK3511294 and placebo.

AESI of QTc prolongation will be summarised as detailed in Section 4.6.3.3 ECG.

Separate listings of AESIs identified by the investigator as anaphylaxis, allergic (type I hypersensitivity), other systemic reactions, vasculitis events and local injection site reactions will be produced. Patient profile of on treatment adverse events of vasculitis will also be listed.

4.6.3. Additional Safety Assessments

4.6.3.1. Laboratory Data

Summaries of laboratory data including chemistry and haematology parameters, and liver chemistry test data will be based on GSK Core Data Standards and unless otherwise specified will include on-treatment and post-treatment data.

A scatter plot of maximum post-baseline ALT vs maximum post-baseline total bilirubin will be produced. In addition, if any liver stopping or liver monitoring events occur during the study, summaries of liver monitoring/stopping event reporting and hepatobiliary laboratory abnormalities will be produced.

Samples for anti-MPO antibody, anti-PR3 antibody, ANA, and antidsDNA antibody are collected at baseline visit and if clinically indicated post baseline, analysed on as needed basis and will be summarised only for participants with data available.

The details of the planned displays will be in OPS.

4.6.3.2. Vital Signs

Pre-dose systolic blood pressure, diastolic blood pressure, pulse rate and body temperature including change from baseline at all visits will be summarised and listed.

4.6.3.3. ECG

Actual and change from baseline (for post-baseline timepoints) values for QTc(F), and heart rate will be summarised by treatment for Screening, Baseline, Week 26, Week 52, and withdrawal visit. ECG results will also be listed. Abnormal findings and interpretations will be listed separately.

Individual maximum QTc(F) values will also be summarised to show the number of subjects with maximum values (msec) in the following categories: <= 450, 450 < to <= 480, 480 < to <= 500 and > 500.

Additionally, individual maximum changes from baseline in QTc(F) values will be summarised to show the number of subjects with maximum changes (msec) in the categories: < -60, ≥ -60 to < -30, ≥ -30 to < 0, ≥ 0 to < 30, ≥ 30 to < 60 and ≥ 60.

All ECG values for participants with protocol defined QT stopping criteria will be listed.

4.6.3.4. Complement

Complement (C3 and C4) will be summarised by parameter and visit and presented as a table and as a figure. The summary table will include baseline concentration, concentrations at each visit and ratio to baseline at each visit. Summary statistics to be presented are n, geometric mean, SD of logs, median, minimum and maximum.

4.7. Immunogenicity Analysis

For the immunogenicity assessment, two types of anti-drug antibody (ADA) assays will be performed, a binding antibody assay and a neutralizing antibody assay (NAb).

For the binding assay, there will be a three-tiered analysis: screening, confirmation and titration. The screening assay produces a result of positive or negative relative to a screening cut point. Positive samples continue with the confirmation assay, which also produces a result of positive or negative relative to a confirmation cut point. For positive confirmation samples, a titre value will also be obtained to quantify the degree of binding in a titration assay, and the sample will be tested with the neutralizing assay, which also reports results as positive or negative. A sample that is positive in the confirmation assay is considered positive for anti-GSK3511294 antibodies.

All participants' baseline immunogenicity samples will be analysed. Post-baseline immunogenicity samples will only be analysed for participants receiving GSK3511294 100 mg SC.

The following descriptive summaries will be presented for GSK3511294 100 mg SC group by visit using mITT population.:

- Summary of binding antibody assay results: it will summarise the binding antibody confirmatory assay results at each visit. Summary will include categories for negative and positive results, sub categories for transient positive and persistent positive (see note below), and available titre values (min, median and max). It will also summarise the highest post-baseline binding antibody confirmatory assay result obtained.
- Summary of binding antibody results for participants without positive result prior to dosing: it will summarise the binding antibody confirmatory assay results at each visit. Summary will include categories for negative and positive results, sub categories for transient positive and persistent positive (see note below), and available titre values (min, median and max). It will also summarise the highest post-baseline binding antibody confirmatory assay result obtained.
- Summary of neutralizing antibody assay results: it will summarise the neutralising antibody assay results for participants with a positive binding antibody confirmatory assay results. Neutralising antibody assay results will be categorised as positive or negative. It will also summarise the highest post-baseline neutralizing antibody assay result obtained.
- Summary of AE by highest post-baseline binding antibody confirmatory assay result

The following descriptive summaries will be presented for the placebo group using mITT population:

- Summary of binding antibody assay results for all baseline visit results. Summary will include categories for negative and positive results, and available titre value (min, median and max).

- Summary of neutralizing antibody assay results for all baseline visit results. Summary will include categories for negative and positive results.

Note: Visits will include pre-dose baseline visit and all post-baseline visits where immunogenicity assessments were performed. The binding antibody confirmatory assay results are categorised as negative or positive. The positive results will have two sub categories: transient positive (defined as a single confirmatory positive immunogenic response that does not occur at the final study assessment) or persistent positive (defined as a confirmatory positive immunogenic response for at least 2 consecutive assessments or a single result at the final study assessment). For the summary of highest post-baseline binding antibody confirmatory assay result and neutralizing antibody assay result, subjects with both positive and negative results will be identified in the positive category. If a subject had titre results that fall into multiple titre result categories, they will be included in the highest category.

Immunogenicity data will be listed for participants with at least one positive screening binding antibody assay result.

4.8. Healthcare Resource Utilization

The total number of visits per participant for each type of healthcare contact: non inpatient (home visits [day], home visits [night], physician office/clinic visits, urgent care/outpatient clinic visits, emergency room visits, telephone calls, telemedicine consultations) and inpatient admissions (intensive care unit and general hospital wards) will be presented by summarising the respective visits and number of days (Length of Stay-LOS). This will also be summarised for each contact type (asthma-exacerbations, other healthcare contact).

4.9. Interim Analyses

No interim analyses of efficacy data are planned.

An independent data monitoring committee (IDMC) will periodically review unblinded safety data from the three Phase III studies in the program: 206713 (this study), 213744 and 206785, in accordance with the IDMC Charter.

The IDMC will review all safety data, including AEs and serious adverse events (SAEs) and adverse events of special interest (AESI), laboratory parameters, including haematological and clinical chemistry parameters and ECG assessments from the three studies for identification of any potential safety signals. The safety data analyses for the IDMC reviews will be performed by an independent statistician. There are no circumstances under which IDMC review of the data would lead to a recommendation to stop for efficacy. Other than the emergency unblinding procedures described in the protocol, all personnel having direct responsibility for the conduct of the study will remain blinded to treatment groups for all data until the database is frozen.

4.10. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol (Dated: 01-OCT-2020) are detailed in Table 4.

Table 4 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
Safety population is defined for safety analysis	No safety population is defined	Safety population defined in the protocol is the same as the mITT population. mITT population will be used for safety analysis
Protocol Section 9.3 states actual intervention received will be used in the analysis	Randomised intervention will be used in the analysis	Participants will receive randomised intervention at week 26 and 52 only. It is feasible to use randomised intervention in analysis.

5. SAMPLE SIZE DETERMINATION

Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125).

5.1. Sample Size Assumptions

A sample size of 375 participants (2:1 GSK3511294 to placebo allocation ratio) is based on sufficient power to conclude superiority on primary and key secondary endpoints.

5.1.1. Primary Endpoint

The assumed true annualised rate of exacerbations in the placebo arm is 1.18. Based on an assumed true treatment difference of a 50% reduction in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC, a sample size of 375 randomised participants (250 to GSK3511294, 125 to placebo) will provide 99% power for the primary endpoint at a 5% two-sided significance level [PASS, 2020].

The assumptions for the placebo rate and treatment effect are median values from an elicitation exercise which used Phase 3 anti-IL-5/5R historical data (~50% reduction in exacerbations) and expert opinion. The sample size is based also on an assumption of 0.8 for the dispersion parameter which was observed in two mepolizumab studies Pavord, 2012; Ortega, 2014]. It was assumed that 14% of participant-years data will be missing due to study withdrawal, which is also consistent with mepolizumab studies.

Based on the assumptions above, the minimum observed treatment difference estimated to result in significance at the 5% two-sided significance level is a 27% reduction in exacerbations for GSK3511294 + SoC compared with placebo + SoC (rate ratio of 0.73).

5.1.2. Secondary Endpoints

Table 5 describes the assumptions and power values for two key secondary endpoints. The assumptions are obtained from the Phase 3 mepolizumab studies [Pavord, 2012; Ortega, 2014; Chupp, 2017].

Table 5 Power Calculations for Key Secondary Endpoints

Endpoint	Assumed treatment difference (GSK3511294 + SoC vs. placebo + SoC)	Standard deviation	Power
Change from baseline in SGRQ total score at Week 52	-7	17	96%
Change from baseline in ACQ-5 score at Week 52	-0.35	1.1	83%

5.2. Sample Size Sensitivity

The sample size and power calculations are based on assumptions about the true values for parameters. The power of the study is dependent on changes in these assumptions, in particular the assumed annualised exacerbation rates. Table 6 illustrates how changes in assumptions for two parameters (placebo + SoC annualised exacerbation rate and treatment effect) affect the power.

Table 6 Estimates of Power for Assumed Placebo + SoC Exacerbation Rate and Assumed Percent Reduction with GSK3511294 + SoC Compared with Placebo + SoC

Percent reduction in annualised exacerbation rate with GSK3511294 + SoC vs. placebo + SoC	Placebo + SoC annualised exacerbation rate			
	1.0	1.1	**1.18**	1.3
30%	61	63	65	67
40%	88	90	91	92
50%	98	99	**99**	99

5.3. Sample Size Re-estimation or Adjustment

There will be no sample size re-estimation.

There is a possibility for randomising greater than 375 participants in the study. This is due to local country requests or requirements, for example, the local health authority specifying a minimum number to be enrolled. The primary analysis and clinical study report (CSR) will be based on the initial target enrolment. If the study target enrolment is reached before a local country enrolment requirement is met, then recruitment in that country may continue. Participants from those countries, who have already been enrolled

at the time of reaching the target enrolment, will be included in the primary analysis. All data (pre- and post-target enrolment) will be analysed together but reported later in a supplement to the study report. Inferences will be drawn on the original study report based on the target enrolment.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Abbreviations and Trademarks

6.1.1. List of Abbreviations

Abbreviation	Description
ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
ADSD	Asthma Daily Symptom Diary
ANSD	Asthma Nightly Symptom Diary
AE	Adverse Event
AESI	Adverse Event of Special Interest
Anti-IL-5	Anti-Interleukin-5
BP	Blood pressure
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPMS	Clinical Pharmacology Modeling and Simulation
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case report form
ED	Emergency Department
eDiary	Electronic diary
FEV1	Forced expiratory volume in 1 second
GSK	GlaxoSmithKline
HRQoL	health-related quality of life
ICS	Inhaled corticosteroids
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IL-5	Interleukin-5
LOS	Length of Stay
IM	Intramuscular
IV	Intravenous
KR method	Kenward and Roger method
LS Mean	Adjusted mean for the treatment group
LS Mean Change	Adjusted mean change from baseline for the treatment group
MAR	Missing at Random
MNAR	Missing Not at Random
Max	Maximum
MedDRA	Medicinal dictionary for regulatory activities

Abbreviation	Description
Min	Minimum
mITT	Modified Intent to Treat
Mg	Milligram
MMRM	Mixed Models Repeated Measures
NAb	Neutralising antibody
NHANES	National Health and Nutrition Examination Survey
OCS	Oral corticosteroids
OPS	Output and Programming Specification
OR	Odds ratio
PD	Pharmacodynamics
PEF	Peak expiratory flow
PT	Preferred Term
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PRO	Patient-reported outcomes
PROMIS	Patient-reported outcomes measurement information system
QTcF	QTc corrected by Fridericia's formula
RAP	Reporting and Analysis Plan
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SAC	Statistical Analysis Complete
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SGRQ	St George's Respiratory Questionnaire
SNOT-22	Sino-nasal Outcomes Test-22
SoC	Standard of care
SOC	System Organ Class

6.1.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

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Protocol: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

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Statistical Analysis Plan Amendment 2

Study ID: 206713

Official Title of Study: A 52-week, randomised, double-blind, placebo-controlled, parallelgroup, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

NCT ID: NCT04719832

Date of Document: 14-DEC-2023

Division	:	Worldwide Development
Information Type	:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 (Depemokimab) adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Protocol Number: 206713

Compound Number: GSK3511294

Short Title: Placebo-controlled efficacy and safety study of GSK3511294 (Depemokimab) in participants with severe asthma with an eosinophilic phenotype

Acronym: SWIFT-1

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
IND	**146742**
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SAP Author(s):

Author
PPD Principal Statistician, Dev Biostats Stats Dev
PPD Statistical Leader, Dev Biostats Stats Dev

SAP Biostatistics Line Approval (Pharma TMF eSignature):

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VERSION HISTORY

Table 1 SAP Version History Summary

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1	22-Jan-2021	Version 01 Approval Date: 01-OCT-2020	Not Applicable	Original version

Amendment 01	02-Aug-22	Amendment 02 Approval Date: 08-APR 2022	1. Section 1.1.2 Estimand: updated intercurrent event strategy for change in maintenance therapy	1. Different strategies to be applied to intercurrent event of change in maintence therapy and use of prohibited medication for PD endpoint. Also added clarification for this intercurrent event.
			2. Section 3 Analysis Sets: Updated text related to enrolled, randomised, full analysis set, and safety population. Added China sub-population.	2. Revision of Analysis sets based on the new SAP template description. To included China reporting into this analysis plan.
			3. Section 4.3.2: updated model checking method	3. Correct the checking method
			4. Section 4.4.9: removed statistical analysis of PGI-P/PGI-C endpoints	4. Only need summary
			5. Section 4.4.10 ADSD/ANSD: added study 217640	5. Clarification
			6. Section 4.5.2: updated imputation method for non-detectable blood eosinophil values of 0 GI/L, or results below the limit of quantification.	6. Clarification
			7. Section 4.6.3.3: adding two visits for ECG reporting and modified wording for categories to be reported	7. Update due to protocol amendment
			8. Section 4.9: Added unblinded interim analysis for futility and blinded analysis for validation of questionaries	8. Update due to protocol amendment
			9. Section 4.10: removed that Table of 'Changes to Protocol Defined Analyses'.	9. Update due to protocol amendment
			10. Section 4.4.15: added a summary of systemic corticosteroids use associated with clinically significant exacerbations	10. Update in order to include all type of corticosteroids use

Amendment 02	14-Dec-2023	Amendment 02 Approval Date: 05-APR 2022	1. Section 1.1.1 Endpoints and Section 2.1 Multiplicity Adjustment	1. Based on FDA's feedback that for ADSD/ANSD measures to be considered for inclusion in the label they should be elevated in the hierarchy (as secondary endpoints).
			2. Section 1.1.2:updated for the endpoints with descriptive summaries, changed from 'while on treatment strategy' to 'hypothetical strategy. And removed safety endpoints from the table.	2. Clarification.
			3. Section 3 updated FAS and Safety analysis sets . Added FAS-modified and Safety-modifitied analysis sets.	3. To exclude patients from the site that had GCP non-compliance for the main analyses.
			4. Section 4.1.2 Baseline Definition: changed from 'Day -7 to Day 1' to 'Day -6 to Day 1'	4. Clarification
			5. Section 4.2.2, 4.3.2, 4.4, Main Analytical Approach, removed the covariate of ' baseline maintenance OCS therapy (OCS vs. no OCS)' from the analysis model	5. This covariate is not needed because >95% subjects were not on maintenance OCS therapy at baseline.
			6. Section 4.2.3.2 removed condition for performing tipping point sensitivity analysis	6. Tipping point analysis will be performed regardless proportion of missing data
			7. Section 4.4.10.2. Added analysis for responder based ADSD/ANSD	7. as planned since MCID for ADSD/ANSD becomes available
			8. Section 4.4.13. Added a PEF plot	8. a figure is needed for CSR
			9. Section 4.4.15. Removed the summary of number of days with systemic corticosteroids (including OCS, IV and IM) use	9. data shows there is very limited number of IV or IM systemic corticosteroids usage
			10. Section 4.9 added the section for Risk Benefit forest plot	10. additional plot required for CSR
			11. Section 4.3.2, 4.4.3, 4.4.10 added suggestion for how to exclude timepoints from analysis when the model does not converge.	11. Clarification
			12. Section 4.10 added clarification for analyses on China subpopulation	12. Clarification
			13. Section 4.1.1 added clarification for covaiates	13. Clarification

			14. Section 4.3.3 added condition for performing analysis	14. Clarification

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 206713. Details of the planned final analyses are provided.

Descriptive study population analyses such as summary of demography and baseline characteristics and additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Change from baseline in Asthma Daily Symptom Diary (ADSD)/ Asthma Nightly Symptom Diary (ANSD) weekly mean score at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks
Other	
• To investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	• Time to first clinically significant exacerbation[a] • Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit • Change from baseline in SGRQ total

Objectives	Endpoints
	score at discrete timepoints during the 52-week period • Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period • SGRQ total score responder status at Week 52 (responder defined as achieving ≥4-point reduction from baseline) • ACQ-5 score responder status at Week 52 (responder defined as achieving ≥0.5-point reduction from baseline) • Change from baseline in Patient-Reported Outcomes Measurement Information Systems (PROMIS) Fatigue items score at discrete timepoints during the 52-week period • Change from baseline in Asthma Daily Symptom Diary (ADSD)/ Asthma Nightly Symptom Diary (ANSD) weekly mean score at specified timepoints during the 52-week period • ADSD responder status (responder defined as achieving ≥1.2 point reduction from baseline) over the 52-week period • ANSD responder status (responder defined as achieving ≥1.5 point reduction from baseline) over the 52-week period • Change from baseline in awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean • Change from baseline in morning peak expiratory flow (PEF) 2-week mean • Change from baseline in daily asthma symptom scores 2-week mean • Change from baseline in mean number of occasions of rescue medication use/day 2-week mean • Mean number of days with oral corticosteroids (OCS) usage over 52 weeks • Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints

Objectives	Endpoints
	during the 52-week period • Change from baseline in Sino-nasal Outcomes Test-22 (SNOT-22) score at discrete timepoints during the 52-week period
• To investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient- and clinician-rated response to therapy • patient global impression of asthma severity and its change from baseline	• Patient-rated response to therapy at discrete timepoints during the 52-week period • Clinician-rated response to therapy at discrete timepoints during the 52-week period • Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period • Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during the 52-week period
• To investigate the PD effects of GSK3511294	• Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period
• To investigate the PK of GSK3511294	• GSK3511294 plasma concentration at discrete timepoints during the 52-week period
Safety	
• To evaluate the safety and tolerability of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Incidence of AEs/SAEs • Laboratory parameters, including haematological and clinical chemistry parameters • Vital signs including blood pressure (BP), body temperature, and pulse rate • ECG assessments • Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294
Health Resource Use	
• To further evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on healthcare utilisation on top of existing asthma therapy	• Healthcare utilisation for asthma including hospitalisation, ED, and physician office/clinic visits

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of systemic

Objectives	Endpoints
	corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit. For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

1.1.2. Estimands

Table 2 Estimands

The following two attributes apply to all estimands:

- Treatment comparison: GSK3511294 + SoC compared with placebo + SoC
- Population: Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Objectives	**Estimand**		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
Primary objective: To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	Annualised rate of clinically significant exacerbations over 52 weeks	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred • Change in maintenance therapy (not important PDs):	Ratio of the rates of exacerbations between GSK3511294 + SoC and placebo + SoC.

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	
Secondary objective: to evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	a) Change from baseline in SGRQ total score at Week 52 b) Change from baseline in ACQ-5 score at Week 52 c) Change from baseline in pre-bronchodilator FEV_1 at Week 52	• Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be handled with a hypothetical strategy i.e. had the intercurrent event not occurred	a) Difference in mean change from baseline in SGRQ total score at Week 52 between GSK3511294 + SoC and placebo + SoC b) Difference in mean change from baseline in ACQ-5 score at Week 52 between GSK3511294 + SoC and placebo + SoC c) Difference in mean change from baseline in pre-bronchodilator FEV_1 at Week

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	d) Change from baseline in ADSD/ ANSD weekly mean score at Week 52 e) Annualised rate of clinically significant exacerbations requiring hospitalisation and/or ED visit over 52 weeks	• Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	52 between GSK3511294 + SoC and placebo + SoC d) Difference in mean change from baseline in ADSD/ ANSD weekly mean score at Week 52 between GSK3511294 + SoC and placebo + SoC e) Ratio of the rates of clinically significant exacerbations requiring hospitalisation and/or ED visit between GSK3511294 + SoC and placebo + SoC
Other objective: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	a) Time to first clinically significant exacerbation b) Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons	a) Hazard ratio of first clinically significant exacerbation between GSK3511294 + SoC and placebo + SoC b) Hazard ratio of first clinically significant exacerbation requiring hospitalisation and/or ED visit between GSK3511294

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	c) Change from baseline in SGRQ total score at discrete timepoints during the 52-week period d) Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period e) Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period f) Change from baseline in Sino-nasal Outcomes Test-22 (SNOT-22) score at discrete timepoints during the 52-week period	related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred • Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	+ SoC and placebo + SoC c) Difference in mean change from baseline in SGRQ total score at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC d) Difference in mean change from baseline in ACQ-5 score at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC e) Difference in mean change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC f) Difference in mean change from baseline SNOT-22 score at

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	g) Change from baseline in ADSD/ANSD weekly mean score at specified timepoints during the 52-week period		discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC g) Difference in mean change from baseline in ADSD/ ANSD weekly mean score between GSK3511294 + SoC and placebo + SoC
• **Other objective**: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	a) SGRQ total score responder status at Week 52 (responder defined as achieving ≥4-point reduction from baseline) b) ACQ-5 score responder status at Week 52 (responder defined as achieving ≥0.5-point reduction from baseline)	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical	a) Odds ratio in SGRQ total score responder status at Week 52 between GSK3511294 + SoC and placebo + SoC b) Odds ratio in ACQ-5 score responder status at Week 52 between GSK3511294 + SoC and placebo + SoC

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	c) ADSD responder status (responder defined as achieving ≥1.2 point reduction from baseline) over the 52-week period d) ANSD responder status (responder defined as achieving ≥1.5 point reduction from baseline) over the 52-week period	strategy i.e. had the intercurrent event not occurred. Status following IE will be set as missing. • Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	c) Odds ratio in ADSD responder status over 52 weeks between GSK3511294 + SoC and placebo + SoC d) Odds ratio in ANSD responder status over 52 weeks between GSK3511294 + SoC and placebo + SoC
• **Other objective**: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of	a) Change from baseline in PROMIS Fatigue items score at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy	a) Descriptive summary of change from baseline in PROMIS Fatigue items score by treatment group and by visit

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	b) Change from baseline in awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean c) Change from baseline in morning peak expiratory flow (PEF) 2-week mean d) Change from baseline in daily asthma symptom scores 2-week mean e) Change from baseline in mean number of occasions of rescue medication use/day 2 week mean	strategy i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred. • Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	b) Descriptive summary of change from baseline in 2-weekly mean awakenings at night due to asthma symptoms requiring rescue medication use by treatment group and by time interval e) Descriptive summary of change from baseline in 2-week mean morning PEF by treatment group and by time interval f) Descriptive summary of change from baseline in daily asthma symptom scores 2-week mean by treatment group and by time interval g) Descriptive summary of change from baseline in 2 week mean number of occasions of rescue medication use/day by

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	f) Mean number of days with oral corticosteroids (OCS) usage over 52 weeks		treatment group and by visit and time interval h) Descriptive summary of mean number of days OCS usage over 52 weeks by treatment group
Other objective: to investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient- and clinician-rated response to therapy	a) Patient-rated response to therapy at discrete timepoints during the 52-week period b) Clinician-rated response to therapy at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred. • Change in maintenance therapy (not important PDs): treatment policy strategy i.e.	Descriptive summary of (by treatment group) a) Patient-rated response to therapy at discrete timepoints during the 52-week period b) Clinician-rated response to therapy at discrete timepoints during the 52-week period

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		regardless of the intercurrent event occurring. Summary will include all on and off treatment data. • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event. occurring. Summary will include all on and off treatment data.	
Other objective: to investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient global impression of asthma severity and its change from baseline	a) Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period b) Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical	Descriptive summary of (by treatment group) a) PGI-S of asthma at discrete timepoints during the 52-week period b) PGI-C from baseline of asthma severity at discrete timepoints during the 52-week period

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		strategy i.e. had the intercurrent event not occurred. • Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	
Other objective: to investigate the PD effects of GSK3511294	Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: while on treatment strategy i.e. only data collected while participant was on-treatment will be used on the analysis. Blood eosinophil	Ratio in absolute blood eosinophil count GSK3511294 + SoC vs. placebo + SoC

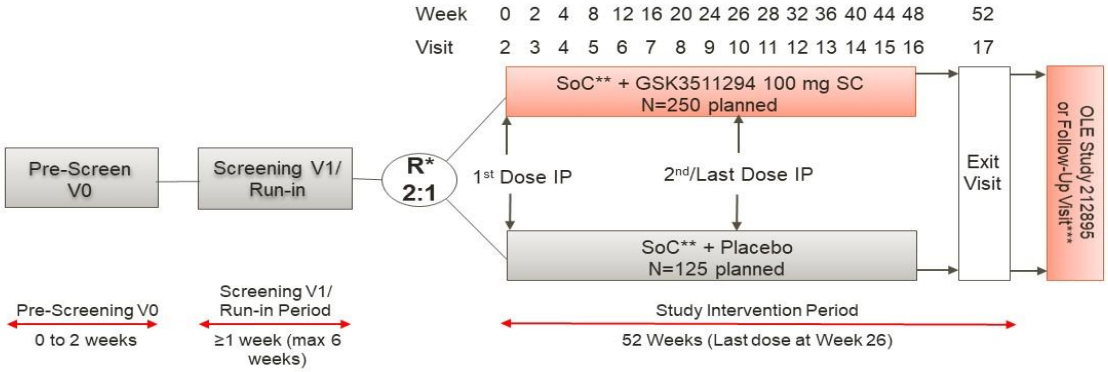
Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		counts taken more than 26 weeks following last dose will not be included in the analysis. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: same as above • Change in maintenance therapy(not important PDs): same as above • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): hypothetical strategy i.e. had the intercurrent event not occurred.	
Other objective: to investigate the PK of GSK3511294	GSK3511294 plasma concentration at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their	Descriptive summarise of GSK3511294 plasma concentration by visit. (GSK3511294 + SoC arm only)

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		randomised treatment. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Change in maintenance therapy(not important PDs): same as above • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): hypothetical strategy i.e. had the intercurrent event not occurred.	
Health Resource Use: To further evaluate GSK3511294 100 mg (SC) every 26 weeks versus	Healthcare utilisation for asthma including hospitalisation (including ICU admissions and Length of Stay-	Same strategy as per primary endpoint	Descriptive summary of healthcare utilisation

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
placebo on healthcare utilisation on top of existing asthma therapy	LOS), ED, and physician office/clinic visits (scheduled and unscheduled)		

1.2. Study Design

Overview of Study Design and Key Features



** R = Randomisation: To be randomised participants without a historical blood eosinophil count of ≥300 cells/μL must have a blood eosinophil count of ≥150 cells/μL at Screening Visit 1. Participants will remain on their standard of care (SoC) asthma therapy throughout the intervention period and will be randomised 2:1 to receive GSK3511294 (100 mg) or placebo.*
*** SoC = medium to high dose ICS (≥440 μg FP HFA daily or clinical comparability) plus additional controller. SoC asthma therapy to exclude biologics.*
**** OLE = Open label extension. Willing participants will continue directly into OLE Study 212895. Participants unwilling to continue will have a follow-up visit 4 weeks after the Exit Visit.*

Design Features	• Phase 3A • 52-week treatment period • Randomised • Double-blind • Placebo-controlled • Parallel group • Multi-centre • Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125). • A sample size of 375 randomised will provide 99% power to demonstrate superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC in annualised rate of clinically significant exacerbations over 52 weeks, based on the true annualised rate of exacerbations in the placebo arm being 1.18 , an assumed true treatment difference of a 50% reduction and at a 5% two-sided significance level. • Participants who receive both doses of study intervention and complete the Exit Visit will be eligible to participate in an open-label extension (OLE) study (Study 212895), during which they will receive two doses of open-label GSK3511294 100 mg SC over another 52 weeks.
Study intervention and Study intervention Assignment	The study will consist of a pre-screen period (0-2 weeks), a run-in period (1-6 weeks), and a study intervention period (52 weeks). After the run-in period, participants will be randomised in a 2:1 ratio using an interactive response technology (IRT) system in a blinded manner to receive either GSK3511294 100 mg or placebo by SC injection. Randomisation will be stratified based on baseline ICS dose (medium or high dose). Two doses of study intervention will be administered in the clinic: the first at randomisation Visit 2 (Week 0) and the

Overview of Study Design and Key Features	
	second at Visit 10 (Week 26). Participants will be assessed at each scheduled visit (a total of 17 study visits) during the 52-week treatment phase. Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 3, Visit 10, Visit 11, Exit Visit 17, and WS Visit (if applicable). Participants will remain on their existing stable maintenance asthma therapy throughout the study.
Interim Analysis	• An unblinded interim analysis for futility is planned • A blinded data analysis is also planned to complete a psychometric analysis of the ADSD/ANSD and PROMIS fatigue items. • Regular IDMC reviews of safety data are planned.

2. STATISTICAL HYPOTHESES

The primary study objective is to test for the superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC, assessed by the annualised rate of clinically significant exacerbations measured over the study intervention period of 52 weeks.

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 and placebo.

2.1. Multiplicity Adjustment

The treatment comparison of interest for the primary and secondary endpoints is GSK3511294 100 mg SC + SoC vs placebo + SoC. A fixed sequence hierarchical testing procedure will be used to provide strong control of Type I error for multiplicity arising from the primary and multiple secondary endpoints. This will be carried out using a stepdown closed testing procedure where inference for an endpoint in the predefined hierarchy will be dependent on statistical significance having been achieved for the previous endpoints in the hierarchy. For example, for the primary endpoint, GSK3511294 + SoC will be compared to placebo + SoC at a two-sided 5% level. The next endpoint in the hierarchy (i.e. the first secondary endpoint) will be tested only if the test for the primary endpoint is significant at the two-sided 5% level. Testing will continue down the hierarchy for the remaining endpoints in an equivalent manner only if the previous endpoint in the hierarchy achieves statistical significance.

The hierarchy of the primary and secondary endpoints to be tested is as follows:

1. Annualised rate of clinically significant exacerbations over 52 weeks
2. Change from baseline in SGRQ at Week 52
3. Change from baseline in ACQ-5 at Week 52
4. Change from baseline in clinic pre-bronchodilator FEV_1 at Week 52
5. Change from baseline in ANSD at Week 52

6. Change from baseline in ADSD at Week 52
7. Annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who sign the ICF.	Study Population
Enrolled	All participants who entered the study. Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Randomised	All participants who were randomly assigned to study intervention in the study.	Study Population
Full Analysis Set (FAS)	All randomised participants who receive at least one dose of study intervention excluding participants from Site 250190. Data will be analysed according to randomised treatment arm.	• Study Population • Efficacy • Immunogenicity • PD • Health Resource Use
FAS-PROMIS	All participants in the FAS population for whom at least one PROMIS fatigue items were administered	• Efficacy (PROMIS)
FAS-ADSD/ANSD	All participants in the FAS population for whom at least one ADSD/ANSD questionnaire were administered	• Efficacy (ADSD/ANSD)
FAS-China	All participants in the FAS population who are enrolled from China	• Study Population • Efficacy •
FAS-Non-China	All participants in the FAS population who are not in FAS-China analysis set	• Not planned in this SAP but flagged for future analysis

Analysis Set	Definition / Criteria	Analyses Evaluated
Safety	All randomised participants who receive at least one dose of study intervention excluding participants from Site 250190. Participants will be analysed according to the intervention they are allocated at randomisation, unless a participant receives a different intervention to the randomised intervention at all protocol-defined administrations at which study medication was received, in which case the participant will be analysed according to the actual intervention they received. This population will serve as the primary population for analyses of safety endpoints.	• Safety
Safety-China	All participants in the Safety population who are enrolled from China	• Safety •
Safety-Non-China	All participants in the Safety population who are not in Safety-China analysis set	• Not planned in this SAP but flagged for future analysis
PK	All participants in the FAS population for whom at least one pharmacokinetic sample was obtained, analysed and was measurable.	• PK
PK-China	All participants in the PK population who are enrolled from China	• PK
PK-Non-China	All participants in the PK population who are not in PK-China analysis set	• PK (flagged for future PK analysis)
FAS-Modified	All participants in the FAS population plus randomised participants from Site 250190 who receive at least one dose of study intervention.	• Efficacy (Primary and Secondary)
Safety-Modified	All participants in the Safety population plus randomised particiants from Site 250190 who receive at least one dose of study intervention. Participants will be analysed according to the intervention they are allocated at randomisation, unless a	• Key Safety

Analysis Set	Definition / Criteria	Analyses Evaluated
	participant receives a different intervention to the randomised intervention at all protocol-defined administrations at which study medication was received, in which case the participant will be analysed according to the actual intervention they received.	
FAS-ADSD/ANSD-Modified	All participants in the FAS-ADSD/ANSD population plus randomised participants from Site 250190 who receive at least one dose of study intervention.	• Efficacy (ADSD/ANSD)

Note: GCP non-compliance/significant data integrity concern at Site 250190 was identified.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The Full Analysis Set (FAS) will be used for all Study Population, Efficacy, Immunogenicity and PD analyses, unless otherwise stated. The Safety analysis set will be used for safety analyses, unless otherwise stated. PK analysis sets will be used for PK data analysis. FAS-China, Safety-China and PK-China will be used for China outputs. The Output and Programming Specification (OPS) document will provide more details.

Confidence intervals will use 95% confidence intervals (CI) unless otherwise specified.

Unless otherwise specified, continuous data will be summarised using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarised as the number and percentage of participants in each category.

For endpoints that are formally modelled, summary statistics will be provided. In the statistical analysis where covariates are included in the modelling, the following approach will be applied:

- The covariate of exacerbation history is classified as 2, 3, 4+. In the event that exacerbation history is <2, it will be included in the category of '2'.

- For the covariate of baseline pre-bronchodilator % predicted FEV1, screening pre-bronchodilator % predicted FEV1 will be used if baseline value is missing. If both

sreeening and baseline pre-bronchodilator % predicted FEV1 are missing, a missing value will be assigned for this covariate.

Where statistical models are used, if there are important departures from the distributional assumptions, transformations of covariates or alternative models may be explored as supporting analyses.

Randomisation is stratified based on baseline ICS dose (medium or high). All statistical models will include this stratum as a covariate. In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the data collected in the CRF, not the assigned stratum at randomization.

Assessments collected at withdrawal visit will be included in summary tables but won't be included in any statistical analysis.

4.1.2. Baseline Definition

Baseline values for visit based assessments and eDiary assessments are defined in Table 3.

Unless otherwise stated, if baseline is missing, no derivation will be performed and baseline will be set to missing.

Table 3 Baseline Definitions & Derivations

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
Efficacy, Health Outcomes and Other			
SGRQ total and domain scores		X	Day 1 pre-dose
ACQ-5		X	Day 1 pre-dose
Pre-bronchodilator FEV_1	X	X	Day 1 pre-dose
Post-bronchodilator FEV_1	X	X	Day 1 pre-dose
PROMIS Fatigue items score		X	Day 1 pre-dose
ADSD/ANSD weekly mean score	X (daily following Screening)		Average of measurements from Day -7 to Day -1 inclusive (at least 4 days must be non-missing)
Awakenings at night due to asthma symptoms requiring	X (daily following Screening)		Average of measurements from Day -7 to Day -1 inclusive (at least 4 days must be non-missing)

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
rescue medication use 2-week mean			
Morning PEF 2-week mean	X (daily following Screening)		Average of measurements from Day -6 to Day 1(pre-dose) inclusive (at least 4 days must be non-missing)
Daily asthma symptom scores 2-week mean	X (daily following Screening)		Average of measurements from Day -6 to Day 1(pre-dose) inclusive (at least 4 days must be non-missing)
Mean number of occasions of rescue medication use/day 2-week mean	X (daily following Screening)		Average of measurements from Day -6 to Day 1(pre-dose) inclusive (at least 4 days must be non-missing)
SNOT-22 score		X	Day 1 pre-dose
PGI-S	X	X	Day 1 pre-dose
Safety			
Blood pressure	X	X	Values from most recent assessment prior to first dose of study treatment which records both systolic and diastolic BP
Pulse rate	X	X	Most recent individual value prior to first dose of study treatment
Clinical Chemistry	X	X	Most recent individual value prior to first dose of study treatment
ECG endpoints	X	X	Values from most recent ECG conducted prior to first dose of study treatment
Hematology with differential (including eosinophil count)	X	X	Most recent individual value prior to first dose of study treatment

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
Other			
Complement C3 and C4		X	Day 1 pre-dose
Immunogenicity		X	Day 1 pre-dose

NOTES :

- Only records that have been assigned a treatment phase of 'pre-treatment' will be considered as baseline assessments.
- ADSD is to be completed before going to bed and refers to asthma symptoms during the day. Day 1 assement of ADSD will not be pre-dose. Therefore an average of measurements from Day -7 to Day -1 is defined as the baseline for ADSD/ANSD.
- Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and Listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

4.1.3. Multicenter Studies

For the purposes of covariate adjustment in the statistical analysis, countries will be grouped into regions. The following regions are defined:

- European (Czechia, France, Germany, Italy, Ireland, Poland, Spain, UK)
- US
- Rest of World (Canada, China, Russia)

If there are insufficient subjects in each region for the statistical procedures to converge satisfactorily, the combining of regions will be considered.

4.2. Primary Endpoint Analyses

4.2.1. Definition of endpoint

The primary endpoint is the annualized rate of clinically significant exacerbations over the 52 weeks following randomisation.

Clinically significant exacerbations of asthma are defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see protocol Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.
Exacerbations recorded in the eCRF are considered as verified clinically significant exacerbations and will be included in the primary analysis.
Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

4.2.2. Main analytical approach

Primary Statistical Analyses
Endpoint(s)
• Annualized rate of clinically significant exacerbations over 52 weeks
Model Specification

• Generalized linear model assuming a negative binomial distribution
• Terms in the model:
  • **Response**: number of recorded clinically significant exacerbations experienced per subject.
  • **Categorical**: treatment group, exacerbation history (variable (2, 3, 4+)), baseline ICS dose (medium, high), geographical region
  • **Continuous**: baseline pre-bronchodilator % predicted FEV_1
  • **Offset**: Log_e(total time in the study in years)

Model Checking & Diagnostics
• The fit of the regression models will be examined using "Q-Q" plots of the standardized residuals. Interpretation of these plots will be aided by the addition of simulation-generated tolerance boundaries.
Results Presentation
• Treatment group model estimated annualized exacerbation rates and associated 95% CI • pairwise treatment rate ratios and associated p-value and 95% CI. • pairwise treatment percent reductions in annual exacerbation rate and associated 95% CI
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed "missing at random" (MAR) (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the primary endpoint, the data for the period following withdrawal will be assumed MAR (based on all data included in the analysis under the current estimand strategy).
Subgroup Analysis
• By baseline ICS dose (medium, high) subgroup analysis will be performed. • Separate model will be fitted for each subgroup.
Additional Analysis
• The same primary endpoint analysis will be performed using FAS-modified analysis set

4.2.3. Sensitivity analyses

For the main analytical approach, data that is missing due to study withdrawal is assumed to be missing at random. The aim of sensitivity analyses is to assess the robustness in the treatment effect and conclusion in the main analytical approach when departing from the missing at random assumption. Two sensitivity analyses will be performed for this investigation.

4.2.3.1. Sensitivity Analysis 1 (MNAR Based on off-treatment Data)

This sensitivity analysis will be performed where subjects who withdrew from the study early will have missing data imputed for the period of time between withdrawal from the study to the Week 52 visit based on the off-treatment data collected from subjects who continued in the study following discontinuation of randomised intervention. Multiple imputation methods will be used with results combined across imputations using Rubin's method [Roger, 2018].

If the total unobserved/excluded time in the study is <3% of the total study duration or if <50% of the total off-treatment period is observed then the sensitivity analysis will not be conducted.

4.2.3.2. Sensitivity Analysis 2 (Tipping Point Analysis)

Tipping point analysis will explore the impact of missing data by using differing assumptions regarding the exacerbation rate in subjects who withdraw from the study. Subjects who withdrew from study early will have missing data imputed for the period of time between withdrawal from the study to the Week 52 visit based on a range of values for the rate of exacerbations per year following study withdrawal. The values to be investigated will be based on increases relative to the estimated rates obtained within each arm under the MAR assumption. The imputed exacerbation rates will vary independently for the active and placebo arms, and will include scenarios where subjects in the active arm have worse outcomes following early withdrawal from the study than subjects in the placebo arm. The tipping point multiple imputation method will be based on pattern mixture models [Keene, 2014]. The results from the analyses of each sample are combined using Rubin's method.

4.3. Secondary Endpoints Analyses

4.3.1. Definition of endpoint(s)

The secondary endpoints are:

- Change from baseline in SGRQ total score at Week 52
- Change from baseline in ACQ-5 score at Week 52
- Change from baseline in pre-bronchodilator FEV_1 at Week 52
- Change from baseline in ANSD at Week 52 (see Section 4.4.10)
- Change from baseline in ADSD at Week 52 (see Section 4.4.10)
- Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks

4.3.2. Main analytical approach for SGRQ total score, ACQ-5 score and pre-bronchodilator FEV_1

Secondary Endpoints Analyses
Endpoint(s)
• Change from baseline in SGRQ total score at Week 52 • Change from baseline in ACQ-5 score at Week 52 • Change from baseline in pre-bronchodilator FEV1 at Week 52
Model Specification
• Mixed Models Repeated Measures (MMRM) model. • Terms in the model: • Response: SGRQ Total score or ACQ-5 score or pre-bronchodilator FEV1 at each visit. • Categorical: treatment group, baseline ICS dose (medium or high), exacerbation history (variable (2, 3, 4+)), geographical region, visit • Continuous: baseline (SGRQ Total score, or ACQ-5 score, baseline pre-bronchodilator % predicted FEV1) • Interaction: baseline*visit, treatment group*visit • Repeated: visit • The MMRM analysis for SGRQ total scores will include data collected at Weeks 4, 12, 26, 40 and 52. • The MMRM analysis for ACQ-5 score will include data collected at Weeks 2, 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48 and 52. In the event the model fails to run due to too many assessments timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest. Suggested order for dropping timepoints is week 44, 20, 36, 16, 32, 48, 24, 28. • The MMRM analysis for pre-bronchodilator FEV1 will include data collected at Weeks 26 and 52. • The model will be fit with an unstructured variance-covariance matrix. • The Kenward and Roger method (KR) for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. In the event the model fails to run using the KR method, then the residual method will be used instead. In the event the model fails to run using residual method and assessments are from many timepoints, timepoints included in the analysis may be reduced by keeping the timepoints/intervals of most interest. • Baseline is defined in Section 4.1.2 • Two models will be fitted; one with a response variable of change from baseline and one with the response variable as the raw value. •
Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
Results Presentation
• Least-square (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI and P-values for each visit will be presented. • The LS mean treatment differences (and associated 95% CIs) for all visits will also be presented graphically. • SGRQ total scores, ACQ-5 score and pre-bronchodilator FEV1 (absolute value and changes from baseline) will also be summarised by treatment group and visit.
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis.

Secondary Endpoints Analyses
Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).
Additional Analysis
The same secondary endpoint analyses will be performed using FAS-modified analysis set

4.3.3. Main analytical approach for annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

The annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks will be analysed using a negative binomial generalised linear model, as described for the primary endpoint, Section 4.2.2 for details. This endpoint would only be analysed in the event that a total of 20 or more exacerbations requiring hospitalisation and/or ED visit occurred in the study.

4.3.4. Sensitivity analyses

The sensitivity analyses for the primary endpoint as described in Section 4.2.3 will also be performed for the secondary endpoints.

4.4. Other Endpoints Analyses

4.4.1. Time to first clinically significant exacerbation and Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit

Other Endpoints Analyses
Endpoint(s)
• Time to first clinically significant exacerbation • Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit
Model Specification
• Cox's proportional hazards model • Terms in the model: **Response**: time to first clinically significant exacerbation or first clinically significant exacerbation requiring hospitalization and/or ED visit **Categorical**: treatment group, exacerbation history (variable (2, 3, 4+)), baseline ICS dose (medium, high), geographical region **Continuous**: baseline pre-bronchodilator % predicted FEV1 • The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead. • Kaplan-Meier survivor functions will be obtained for each treatment group using PROC LIFETEST with a TIME statement.
Model Checking & Diagnostics
• The proportional hazards assumption will be examined by obtaining the Kaplan-Meier estimates of

Other Endpoints Analyses
the survival function S(t) over time separately for each treatment group. In addition, the ln {-ln[S(t)]} plot will be produced.
Results Presentation
• Hazard ratios and the percent reduction in risk for the pairwise treatment comparisons with associated 95% CIs and p-values will be presented. • The Kaplan-Meier curves will be presented showing the probability of having an event over time for each treatment group separately plotted on the same Figure.
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.2. Change from baseline in SGRQ total score and in ACQ-5 score at discrete timepoints during the 52-week period

Analytic approach for change from baseline in SGRQ total score and change from baseline in ACQ-5 score at discrete timepoints during the 52-week period has been included in the secondary endpoints analyse, see Section 4.3.2 for details.

4.4.3. SGRQ total score responder status at Week 52 and ACQ-5 score responder status at Week 52

Other Endpoints Analyses
Endpoint(s)
• Proportion of responders according to SGRQ total score (responder defined as achieving ≥4-point reduction from baseline) • Proportion of responders according to ACQ-5 score (responder defined as achieving ≥0.5-point reduction from baseline)
Model Specification
Generalized linear mixed model • Terms in the model: **Dependent:** response (yes/no) **Categorical:** treatment group, baseline ICS dose (medium or high), exacerbation history (variable (2, 3, 4+)), geographical region, visit, subject **Continuous**: baseline (SGRQ Total score, or ACQ-5 score), baseline pre-bronchodilator % predicted FEV1 **Interaction:** baseline (SGRQ Total score, or ACQ-5 score)*visit, treatment group*visit The model will be fit with an unstructured variance-covariance matrix with one single model to include all visits where the assessment in question is scheduled to be performed. • Computation of confidence intervals for the odds ratios is based on the individual Wald tests. • The analysis of responder based on SGRQ total scores will include data collected at Weeks 4, 12, 26, 40 and 52. • The analysis of responder based on ACQ-5 score will include data collected at Weeks 2, 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48 and 52. In the event the model fails to run due to too many assessments timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest. Suggested order for dropping timepoints is week 44, 20, 36, 16, 32, 8, 48, 24, 28.

Model Checking & Diagnostics
• Pearson residuals will be plotted by using PLOTS=PEARSONPANEL option for the model statement in SAS.
Results Presentation
• Number and percentage of responders and non-responders for each treatment at each visit • Odds ratio for pairwise comparisons with associated 95 % CIs and p-values
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.4. Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1

Analytic approach for change from baseline in pre-bronchodilator FEV_1 at discrete timepoints during the 52-week period has been included in the secondary endpoint analysis of change from baseline in pre-bronchodilator FEV_1 at Week 52, see Section 4.3.2 for details.

Change from baseline in post-bronchodilator FEV_1 at discrete timepoints during the 52-week period will be analyzed in the same approach as for change from baseline in pre-bronchodilator FEV_1.

4.4.5. PROMIS Fatigue items score

PROMIS Fatigue items score and change from baseline in PROMIS Fatigue items score will be summaried by treatment group and visit.

4.4.6. SNOT-22 score

The SNOT-22 questionnaire is administered (post randomisation) at Week 26 and 52. The 22 questions of the SNOT-22 are each graded on a 6-point scale ranging from 0 = ‘no symptoms’ to 5 = ‘as bad as things could be’. The scores for each of the questions are summed to derive the total score which ranges from 0 to 110, with higher scores representing worse quality of life.

Other Endpoints Analyses
Endpoint(s)
• Change from baseline in SNOT-22 total score at Week 26 and Week 52
Model Specification, Model Checking & Diagnostics
• See Model Specification, Model Checking & Diagnostics for secondary endpoints statistical analyses • analysis will include data collected at Weeks 26 and 52.

Model Results Presentation
• See Model Results Presentation for secondary endpoints statistical analyses (Figures will not be presented) • SNOT-22 score (absolute value and changes from baseline) will also be summarised by treatment group and visit.
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.7. Patient-rated response to therapy during the 52-week period

This is an overall evaluation of response to treatment, conducted by the participant at Week 12, 26, 40 and 52 using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse

Patients rated response to therapy will be summarised by treatment group and visit.

4.4.8. Clinician-rated response to therapy during the 52-week period

This is an overall evaluation of response to treatment, conducted by the investigator at Week 12, 26, 40 and 52 using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse
Clinician rated response to therapy will be summarised by treatment group and visit.

4.4.9. Patient Global Impression of Asthma Severity/Change (PGI-S, PGI-C)

Patient Global Impression of Asthma Severity (PGI-S): The participant will complete a PGI-S question at the visits: Randomisation and Screening, Day 1, Week 12, 20, 26, 40, 52. This single global question will ask participants to rate their asthma severity on a five-point scale (no symptoms, mild, moderate, severe, very severe). Responses will be captured electronically.

Patient Global Impression of Change (PGI-C) from Baseline of Asthma Severity: The participant will complete a PGI-C question from baseline of their asthma severity at Week 12, 20, 26, 40 and 52. The single question will ask participants to rate the overall change in their asthma severity compared with Day 1 (randomisation) prior to start of study intervention. The rating will use a five-point scale (much better, a little better, no change, a little worse, much worse) and responses will be captured electronically.

PGI-S and PGI-C responses will be summarised by treatment group and visit.

4.4.10. ADSD/ANSD

The ADSD/ANSD is a 6-item self-administered patient-reported diary developed by the PRO Consortium's Asthma Working Group (in accordance with the Food and Drug Administration's PRO Guidance) to facilitate comprehensive and reliable assessment of asthma symptoms from a patient's perspective which received qualification from the FDA in March 2019 supporting use in drug development as an exploratory measure.

The ADSD/ANSD is intended for use by adults and adolescents (aged 12 years and older) who are diagnosed with asthma to rate the severity of their symptoms in the three core categories: breathing symptoms (wheezing, shortness of breath), chest symptoms (chest tightness, chest pain) and cough.

The ADSD/ANSD must be completed twice daily by the participant daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.:

- The morning diary (ADSD) is to be completed upon waking and refers to asthma symptoms during the night-time.
- The evening diary (ANSD) is to be completed before going to bed and refers to asthma symptoms during the day.

Participants are required to rate the six symptoms at their worst during the respective timeframes using an 11-point numeric rating scale (NRS) ranging from 0 ('None') to 10 ('As bad as you can imagine'). Responses will be captured electronically.

4.4.10.1. ADSD/ANSD Change from Baseline

Secondary and Other Endpoints Analyses
Endpoint(s)
• Change from baseline in Asthma Daily Symptom Diary (ADSD) weekly mean score at timepoints during the 52-week period (weekly up to Week 16 and then every visit) • Change from baseline in Asthma Nightly Symptom Diary (ANSD) weekly mean score at timepoints during the 52-week period (weekly up to Week 16 and then every visit)
Model Specification, Model Checking & Diagnostics
• Similar to model specification, model checking and diagnostics detailed in Section 4.3.2 • Response variable: weekly mean scores • Baseline score is defined in Section 4.1.2 • In the event the model fails to run due to too many assessments timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest. Suggested order for dropping timepoints is every other week prior to week 16. If the model still does not converge, then drop week 44, 20, 36, 32, 48, 24, 28.
Model Results Presentation
• LS means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI and P-values for each Week will be presented. • The LS mean treatment differences (and associated 95% CIs) for all weeks will also be presented graphically. ADSD and ANSD weekly mean absolute score and changes from baseline will also be summarised by treatment group and visit. Summary will include weekly mean score at all visits (including all weeks prior to week 16).
Handling of missing data and data excluded due to intercurrent events
Same approach as described in Section 4.3.2

Additional Analysis
The same secondary endpoint analyses will be performed using FAS-ADSD/ANSD-modified analysis set

4.4.10.2. Responder Based on ADSD/ANSD

Other Endpoints Analyses
Endpoint(s)
• Proportion of responders according to ADSD weekly mean score (responder defined as achieving ≥1.2 point reduction from baseline) • Proportion of responders according to ANSD weekly mean score (responder defined as achieving ≥1.5 point reduction from baseline)
Model Specification
Generalized linear mixed model • Terms in the model: **Dependent:** response (yes/no) **Categorical:** treatment group, baseline ICS dose (medium or high), exacerbation history (variable (2, 3, 4+)), geographical region, visit, subject **Continuous**: baseline weekly mean score (ADSD/ANSD) **Interaction:** baseline weekly mean score (ADSD/ANSD)*visit, treatment group*visit The model will be fit with an unstructured variance-covariance matrix with one single model to include all

Other Endpoints Analyses
visits where the assessment in question is scheduled to be performed. • Computation of confidence intervals for the odds ratios is based on the individual Wald tests. • The analysis of responder will include ADSD/ANSD weekly mean score up to week 16, and then week 20, 24, **26**, 28, 32, 36, 40, 44, 48 and **52**. • In the event the model fails to run due to too many assessments timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest. Suggested order for dropping timepoints is every other week prior to week 16. If the model still does not converge, then drop week 44, 20, 36, 32, 48, 24, 28.
Model Checking & Diagnostics
• Pearson residuals will be plotted by using PLOTS=PEARSONPANEL option for the model statement in SAS.
Results Presentation
• Number and percentage of responders and non-responders for each treatment at each visit • Odds ratio for pairwise comparisons with associated 95 % CIs and p-values
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.11. Mean number of occasions of rescue medication per day

Daily diary data for rescue medication (salbutamol/albuterol) use will be aggregated over 2-week periods, then the mean daily usage, excluding days with missing data, will be calculated for each 2-week period (Weeks 1-2, 3-4,…, 51-52). Data for each 2-week period, and change from baseline for each 2-week period will be summarised by treatment group and visit. For definition of baseline see Section 4.1.2.

4.4.12. Awakenings at night due to asthma symptoms requiring rescue medication use

Awakening at night due to asthma symptoms requiring rescue medication use will be summarised as for rescue medication use, see Section 4.4.11.

4.4.13. Morning peak expiratory flow (PEF)

Morning PEF will be summarised as for rescue medication use, see Section 4.4.11.

The summaries will be for :

1) all data included as per FAS population

2) excluding data where asthma medication was taken within 6 hours prior to PEF assessment

The mean change from baseline and associated 95% CIs in morning PEF at all timepoints for the treatment groups will also be presented graphically (for all data).

4.4.14. Daily asthma symptom scores

Daily asthma symptom score will be summarised as for rescue medication use, see Section 4.4.11.

4.4.15. Number of days with oral corticosteroids

Total number of days of oral corticosteroids (OCS) use over 52 weeks that are associated with clinically significant exacerbations per subject will be summarised by treatment group. Also, number of clinically significant exacerbations, number of clinically significant exacerbations treated with OCS, and mean number of days using OCS per clinically significant exacerbations treated with OCS will be summarised by treatment group.

Number of subjects on maintenance OCS at screening, total number of days of maintenance OCS use over 52 weeks and mean number of days of maintenance OCS use per subject will also be summarised by treatment group.

4.5. CLINICAL PHARMACOLOGY DATA ANALYSES

4.5.1. Pharmacokinetic Analyses

In this study, GSK3511294 plasma concentration are collected at discrete timepoints during the 52-week treatment period. GSK3511294 plasma concentration will be summarised by visit. (GSK3511294 + SoC arm only).

The PK data from this study will be included in a meta-analysis of the PK and PKPD data across all GSK3511294 studies. Details of meta-analysis will be in a separate CPMS. analysis plan.

4.5.2. Pharmacodynamic Analyses - Blood Eosinophils

Blood eosinophil counts will be loge-transformed prior to analysis. Non-detectable blood eosinophil values of 0 GI/L, or results below the limit of quantification will be imputed with a value of 0.005GI/L prior to log transformation.

Ratio to baseline during W52 will be analysed using a MMRM analysis. Model specification, model checking and diagnostics are the same as described for secondary endpoints statistical analyses, see Section 4.3.1. Analysis will include data from all visits that blood eosinophils data is collected. LS Mean (SE) and LS Mean ratio to screening (SE) in each treatment group will be presented. Mean treatment ratio and 95% CI for GSK3511294 vs placebo will also be presented.

Absolute and ratio to baseline blood eosinophil counts will be summarised by treatment group and visit. Only results from the central laboratory will be included in the summary.

4.6. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set unless otherwise specified. Summaries of data will report data according to the nominal visit for which it was recorded. Occurrence of Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESIs), laboratory data, vital signs, and ECGs will be included in data displays in the form of frequency Tables, summary statistics, graphs, and statistical analyses where appropriate.

4.6.1. Extent of Exposure

Two doses of study treatment will be administered during study treatment period: the first at randomisation Visit 2 (Week 0) and the second at Visit 10 (Week 26). Each dose is viewed as providing therapeutic coverage for 26 weeks (182 days). The number of treatments administered and the number of days exposure will be summarised descriptively and listed. Total subject-year exposure will also be presented.

Number of days of exposure to study treatment will be calculated as follow:
Duration of Exposure in Days = (Date of Final Dose) – (Date of First Dose) + 182

Subject years exposure is calculated as follow:

Subject Years Exposure = ((Date of Final Dose) – (Date of First Dose) + 182)/365.25

The exposure summary will also be presented by age subgroup (12-17, 18-64, ≥65).

4.6.2. Adverse Events

Adverse events analyses including the analysis of adverse events (AEs), Serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards.

An overview summary of AEs, including counts and percentages of participants with any AE, AEs related to study intervention, AEs leading to permanent discontinuation of study intervention or withdrawal from study, study intervention related AEs leading to permanent discontinuation of study intervention or withdrawal from study, SAEs, SAEs related to study intervention, fatal SAEs, and fatal SAEs related to study intervention will be produced. These summaries will also be produced by age subgroup (12-17, 18-64, ≥65).

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

The frequency and percentage of AEs will be summarised in two ways: 1) in descending order by System Organ Class (SOC) and Preferred Term (PT), where exposure-adjusted incidence rate will also be summarised. 2) in descending order by PT only.

Common (>=3%) AEs will be summarised by overall frequency and summarised by time to onset.

A separate summary will be provided for study intervention-related AEs. A study intervention-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary Table will include events with the relationship to study intervention as 'Yes' or missing. The summary Table will be displayed in descending order by SOC and PT.

All SAEs will be tabulated based on the number and percentage of participants who experienced the event. Separate summaries will also be provided for study intervention-related SAEs. The summary Tables will be displayed in descending order by SOC and PT.

A study intervention-related SAE is defined as an SAE for which the investigator classifies the relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing data, i.e. the summary Table will include events with the relationship to study intervention as 'Yes' or missing. The summary Table will be displayed in descending order by SOC and PT.

4.6.2.1. Adverse Events of Special Interest

Adverse events of special interest (AESI) for GSK3511294 program include:

- Allergic (Type 1 hypersensitivity) reactions including anaphylaxis

Note: these events will be assessed by the investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis.

- Type III hypersensitivity (immune complex disease/vasculitis) reactions
- Local injection site reactions
- QTc prolongation

AESI reported by the investigator as systemic reactions (further categorised by the investigator as either allergic [type I hypersensitivity] or other systemic reactions and assessed against Sampson criteria for anaphylaxis) are collected via targeted eCRF within the study. Vasculitis events and local injection site reactions are also collected via targeted eCRF within the study.

Separate summary Tables showing the number and percent of subjects with each type of AESI (excluding QTc prolongation) broken down by preferred term will be created.

For each type of AESI (excluding QTc prolongation) a profile summary Table will be produced containing information including, but not limited to, the number of occurrences of the event, event characteristics, time to onset, intensity, outcome and action taken.

A summary of the incidence of serious adverse events and adverse events of special interest (excluding QTc prolongation) will be produced displaying the relative risk and risk difference and their 95% CIs between and GSK3511294 and placebo.

AESI of QTc prolongation will be summarised as detailed in Section 4.6.3.3 ECG.

4.6.3. Additional Safety Assessments

4.6.3.1. Laboratory Data

Summaries of laboratory data including chemistry and haematology parameters, and liver chemistry test data will be based on GSK Core Data Standards and unless otherwise specified will include on-treatment and post-treatment data.

A scatter plot of maximum post-baseline ALT vs maximum post-baseline total bilirubin will be produced. In addition, if any liver stopping or liver monitoring events occur during the study, summaries of liver monitoring/stopping event reporting and hepatobiliary laboratory abnormalities will be produced.

Samples for anti-MPO antibody, anti-PR3 antibody, ANA, and antidsDNA antibody are collected at baseline visit and if clinically indicated post baseline, analysed on as needed basis and will be summarised only for participants with data available.

The details of the planned displays will be in OPS.

4.6.3.2. Vital Signs

Pre-dose systolic blood pressure, diastolic blood pressure, pulse rate and body temperature including change from baseline at all visits will be summarised.

4.6.3.3. ECG

Change from baseline (for post-baseline timepoints) values for QTc(F), and heart rate will be summarised by treatment for Baseline, Week 2,Week 26, Week 28, and Week 52. ECG findings will be summarised by visits.

Individual maximum QTc(F) values will also be summarised to show the number of subjects with maximum values (msec) post-baseline relative to baseline in the following categories: Decrease, no change or increase to <= 450, increase to 450 < to <= 480, increase to 480 < to <= 500, increase to 500< to <=530 and increase to > 530. QT uncorrected values will be summarised to show the number of subjects with maximum values (msec) post-baseline relative to baseline in the following categories: Decrease, no change or increase to <600 and increase to >=600.

Additionally, individual maximum changes from baseline in QTc(F) values will be summarised to show the number of subjects with maximum changes (msec) in the categories: increase of <= 30, increase of 31 to 60 and increase of > 60.

All ECG values for participants with protocol defined QT stopping criteria will be listed.

4.6.3.4. Complement

Complement (C3 and C4) will be summarised by parameter and visit and presented as a Table and as a Figure. The summary Table will include baseline concentration, concentrations at each visit and ratio to baseline at each visit. Summary statistics to be presented are n, geometric mean, SD of logs, median, minimum and maximum.

4.6.4. Additional Safety Analyses

The following additional safety analysis will be provided on Safety-Modified analysis set:

- Overview of all adverse events (including site 250190)

- Summary of on-treatment serious adverse events and adverse events of special interest: incidence, relative risk and risk difference (including sites 250190)

- Listing of all adverse events from site 250190

4.7. Immunogenicity Analysis

For the immunogenicity assessment, two types of anti-drug antibody (ADA) assays will be performed, a binding antibody assay and a neutralizing antibody assay (NAb).

For the binding assay, there will be a three-tiered analysis: screening, confirmation and titration. The screening assay produces a result of positive or negative relative to a screening cut point. Positive samples continue with the confirmation assay, which also produces a result of positive or negative relative to a confirmation cut point. For positive confirmation samples, a titre value will also be obtained to quantify the degree of binding in a titration assay, and the sample will be tested with the neutralizing assay, which also reports results as positive or negative. A sample that is positive in the confirmation assay is considered positive for anti-GSK3511294 antibodies.

All participants' baseline immunogenicity samples will be analysed. Post-baseline immunogenicity samples will only be analysed for participants receiving GSK3511294 100 mg SC.

The following descriptive summaries will be presented for GSK3511294 100 mg SC group by visit using FAS population.:

- Summary of binding antibody assay results: it will summarise the binding antibody confirmatory assay results at each visit. Summary will include categories for negative and positive results, sub categories for transient positive and persistent positive (see note below), and available titre values (min, median and max). It will also summarise the highest post-baseline binding antibody confirmatory assay result obtained.

- Summary of binding antibody results for participants without positive result prior to dosing: it will summarise the binding antibody confirmatory assay results at each visit. Summary will include categories for negative and positive results, sub categories for transient positive and persistent positive (see note below), and available titre values (min, median and max). It will also summarise the highest post-baseline binding antibody confirmatory assay result obtained.
- Summary of neutralizing antibody assay results: it will summarise the neutralising antibody assay results for participants with a positive binding antibody confirmatory assay results. Neutralising antibody assay results will be categorised as positive or negative. It will also summarise the highest post-baseline neutralizing antibody assay result obtained.
- Summary of AE by highest post-baseline binding antibody confirmatory assay result

The following descriptive summaries will be presented for the placebo group using FAS population:

- Summary of binding antibody assay results for all baseline visit results. Summary will include categories for negative and positive results, and available titre value (min, median and max).
- Summary of neutralizing antibody assay results for all baseline visit results. Summary will include categories for negative and positive results.

Note: Visits will include pre-dose baseline visit and all post-baseline visits where immunogenicity assessments were performed. The binding antibody confirmatory assay results are categorised as negative or positive. The positive results will have two sub categories: transient positive (defined as a single confirmatory positive immunogenic response that does not occur at the final study assessment) or persistent positive (defined as a confirmatory positive immunogenic response for at least 2 consecutive assessments or a single result at the final study assessment). For the summary of highest post-baseline binding antibody confirmatory assay result and neutralizing antibody assay result, subjects with both positive and negative results will be identified in the positive category. If a subject had titre results that fall into multiple titre result categories, they will be included in the highest category.

4.8. Healthcare Resource Utilization

The total number of visits per participant for each type of healthcare contact: non inpatient (home visits [day], home visits [night], physician office/clinic visits, urgent care/outpatient clinic visits, emergency room visits, telephone calls, telemedicine consultations) and inpatient admissions (intensive care unit and general hospital wards) will be presented by summarising the respective visits and number of days (Length of Stay-LOS). This will also be summarised for each contact type (asthma-exacerbations, other healthcare contact).

4.9. Risk Benefit Analyses

A forest plot will be produced to display efficacy and safety data from analyses in adjacent panels using Full Analysis Set.

The efficacy results will include primary endpoint (and its associated endpoint), i.e. clinically significant exacerbations (and exacerbations requiring hospitalisation and/or ED visit). The AE results will be obtained from the analyses as described in Section 4.6.2.1for the following categories of AEs:

- On-treatment SAE
- Systemic Reactions
  - Allergic (Type 1 hypersensitivity) reactions
    - Anaphylaxis
  - Other systemic reactions
- Type III hypersensitivity/vasculitis
- Local injection site reactions

4.10. Analyses on China Subpopulation

The key study population, efficacy, safety and PK analyses and some exploratory analyses will be repeated in the following subpopulations (as defined in Section 3, Analysis Sets) respectively:

FAS-China： All participants in the FAS population who are enrolled from China.

Safety-China: All participants in the Safety population who are enrolled from China.

PK-China: All participants in the PK population who are enrolled from China.

The subpopulation analyses will employ the same model as the overall population analyses. For MMRM analyses, once the model cannot converge from original settings (including repeated visits and covariates in the models), those will be adjusted to ensure model convergence and obtain stable estimations. For secondary endpoint ACQ-5 including data collected at Weeks 2, 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48 and 52, in the event the model fails to run due to too many assessment timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest. Suggested order for dropping timepoints is week 44, 20, 36, 16, 32, 8, 48, 24, 28.

4.11. Interim Analyses

There will be one unblinded interim analysis for futility. In addition, one blinded analysis for validation of ADSD/ANSD and PROMIS fatigue items will be performed. Periodic review of safety data by an independent data monitoring committee (IDMC) will also be performed. Other than the emergency unblinding procedures described in the protocol, all personnel having direct responsibility for the conduct of the study will remain blinded to treatment groups for all data until the database is frozen.

4.11.1. IDMC Safety Review

IDMC will periodically review unblinded safety data from the three Phase III studies in the severe asthma program: 206713 (this study), 213744 and 206785, in accordance with the IDMC Charter. IDMC will also review safety data from study 212895, an open-label extension study including participants who were previously enrolled in study 206713 or 213744 when sufficient data is collected.

The IDMC will review all safety data, including AEs and serious adverse events (SAEs) and adverse events of special interest (AESI), laboratory parameters, including haematological and clinical chemistry parameters and ECG assessments from the three studies for identification of any potential safety signals. The safety data analyses for the IDMC reviews will be performed by an independent Statistical Data Analysis Centre (SDAC).

4.11.2. Unblinded Interim Analysis for Futility

An unblinded interim analysis for futility will be conducted by an independent SDAC in conjunction with an IDMC to maintain study integrity.

The futility analysis will evaluate efficacy based on the primary endpoint of annualised rate of clinically significant exacerbations using interim data from Phase III studies 206713 (this study) and 213744 when approximately 675 participants are randomised across both studies. The stopping rule is binding, i.e. if the stopping criteria is met then the recommendation will be to stop, conditional on the IDMC deeming that there is no delayed onset of clinical efficacy. Should it be judged that there is delayed onset then this may invalidate an assumption of the interim analysis that the pre-interim data is reflective of post-interim data which could result in inflation of type 2 error. In such a situation, the IDMC will use their expert judgment in determining their recommendation.

Recruitment into the study will continue whilst the futility analysis is taking place. Any communication to the sites regarding the decision will only take place if a decision to stop the study is made. Should the studies be stopped, all on-going participants will complete their follow-up period but will not receive any further doses whilst no further participants will be recruited into the study.

The full details of the process are included in IDMC Charter.

4.11.2.1. Decision Rule

The interim analysis will be based on the predictive probability of meeting the end of study (program) success criteria (defined as statistical significance at a two-sided 5% alpha level in **both** studies 206713 and 213744). Should the predictive probability of success be less than or equal to 0.25 then the studies will be stopped for futility.

The futility rule:

Futility	Continue
Predictive probability (statistical significance two-sided 5%) in **both** 206713 & 213744) ≤ 0.25	Predictive probability (statistical significance two-sided 5%) in **both** 206713 & 213744) > 0.25

4.11.2.2. Methodology

Predictive probability of success will be used to determine the decision of futility or continue. The methodology involves predicting the remainder of the data on the primary endpoint for participants that have not yet completed or yet to be randomised into the study. The primary analysis is then performed separately for each study on this "complete" dataset, i.e. comprising of observed pre-interim data and predicted post-interim data. The success criteria is applied at this stage. To account for uncertainty attached to parameters at the interim, and therefore uncertainty in the predicted remaining data (due to the limited data), this step is performed 1000s of times. The proportion of iterations that meet the success criteria (statistical significance in both studies) gives the predictive probability of success. If this is low (≤0.25), the studies will stop for futility Specific steps on the methodology are given below.

1. Data on the primary endpoint (number of clinically significant exacerbations) will be pooled across the two pivotal studies (206713, 213744) for the purposes of predicting post-interim data. Pooling allows for a more precise estimate of the overall treatment effect resulting in improved operating characteristics. Since these are replicate studies the pooling is deemed appropriate. Participants with at least one month of time in the study since randomisation will be included in the interim analysis (the negative binomial model accounts for varying follow-up time across participants).
2. The primary analysis with pooled data across both studies will be fitted (plus an additional fixed term for study) in a Bayesian framework (non-informative priors on all model parameters). Posterior distributions for the β model parameters and k dispersion parameter will be obtained with 1000s of sets of samples (iterations) taken from these posterior distributions which will be shown in the steps below to be used to predict exacerbations in the post-interim period.
3. For each iteration the expected number of exacerbations pre and post-interim is calculated as $\hat{y}_{i,1}$ and $\hat{y}_{i,2}$, respectively, for each participant, *i*. The predictions for post-interim data will be based on the interim posterior distribution. To calculate $\hat{y}_{i,1}$ and $\hat{y}_{i,2}$, the steps are as follows:
    1. The design matrix (*Z*) is multiplied with the set of posterior β samples and then back-transformed (exponentiated) to give expected annualised exacerbation rate for each participant (μ_i) based on the interim data. Note: for participants yet to be randomised, and therefore without values observed for baseline covariates, bootstrapping from already randomised participants will be performed.
    2. The expected exacerbation rate for the pre-interim and post-interim periods are calculated by multiplying μ_i by the pre-interim and post-interim times in the study for the participant: $\hat{y}_{i,1} = \mu_i \times t_{i,1}$ and $\hat{y}_{i,2} = \mu_i \times t_{i,2}$.

3. For the two periods (pre and post-interim), the number of exacerbations within each period is negative binomial. The distribution of one period conditional upon the other, within a participant, is also negative binomial (Keene, Roger , 2014). The negative binomial parameters for the post-interim period are calculated for each participant and set of posteriors samples (iteration):

- $p_{i,2} = \frac{\frac{1}{k}+\hat{y}_{i,1}}{\frac{1}{k}+\hat{y}_{i,1}+\hat{y}_{i,2}}$
- $k_{i,2} = k_1 + count_{i,1}$
- Where k_1 is the sampled dispersion parameter, $count_{i,1}$ is the number of exacerbations for participant *i* in period 1 (pre-interim), *i* is the participant and *j*=1,2 is the period (pre, post-interim).
- Using these parameters, simulate a participant's number of clinically significant exacerbations for post-interim data for each set of posterior samples

4. The pre-interim observed data (one set) will be combined with each set of post-interim data (1000s of sets) to create 1000s of end of study datasets
    1. Each participant's exacerbation count will be the summation of pre-interim observed count (if the participant was randomised at least one month before the interim data cut) plus the post-interim simulated exacerbation count (if the participant did not complete before the interim).
    2. Each participant's length of time in the study will now be the assumed average length of time in the study, which is set at 0.86 years.
5. The primary analysis model is applied to each iteration (dataset), each study separately. The p-value for the treatment effect (rate ratio) will be calculated. For each iteration, if the success criteria (statistical significance at 5% two-sided level for both studies) is met then the iteration is marked as success (flag as 1), or if not then fail (flag as 0).
6. The mean of these success flags in step 7 is calculated to give the predictive probability of success.
7. If the predictive probability of success is ≤0.25 then the futility criteria has been met.

4.11.2.3. Timing and Operating Characteristics

The proposed timing of the futility analysis is when approximately 675 participants have been randomised across the studies. At this time it is estimated that approximately 200 participants will have completed the studies and 500 received both doses (i.e. at least 6 months worth of data). The median follow-up time in the interim analysis is estimated to be 9 months with the information fraction for the primary endpoint estimated to be 60%, where information fraction is calculated as:

.

$$Information\ fraction = \frac{\sum_{i=1}^{n(interim)} length\ of\ time\ in\ study\ \boldsymbol{at\ interim}_i}{\sum_{i=1}^{750} length\ of\ time\ expected\ i\boldsymbol{n\ complete\ study}_i}$$

Table 4 shows operating characteristics of the futility analysis for a range assumed true treatment effects when approximately 725 participants have been randomised (proposed interim timing). Operating characteristics were obtained by simulating 5,000 studies and following the steps in Section 4.11.2.2 for each simulated study. Operating characteristics are obtained from the aggregate of these simulations.

As this is a futility analysis and there is no opportunity to stop for efficacy the type 1 error (calculated under the null hypothesis of assumed rate ratio = 1) is controlled well below the 5% level. The power of each study is approximately 99%, compared with >99% in the scenario where there is no futility analysis (as described in the protocol). The expected observed rate ratio at the interim to trigger futility is expected to be approximately 0.70.

Table 4 Operating Characteristics of Futility Analysis

Assumed treatment effect (rate ratio depemokimab vs. placebo)	Probability of success (statistical significance in both studies)	Power[1]: 206713	Power[1]: 213744	Probability of futility
1	<0.01	<0.01	<0.01	0.98
0.9	0.01	0.04	0.02	0.94
0.8	0.08	0.18	0.13	0.76
0.7	0.37	0.50	0.44	0.42
0.6	0.78	0.85	0.82	0.11
0.5	0.98	0.98	0.98	0.01

[1] at two-sided 5% significance level for end of study test and incorporating the possibility of futility

4.11.2.4. Outputs

- An interim analysis-specific output presenting the predicted probability of success at the interim
- An interim analysis-specific output presenting model-adjusted annualised exacerbation rate ratio for depemokimab compared to placebo by time period (< 3 months since randomisation, 3 – 6, 6 – 9, 9 – 12)
- Kaplan-Meier plot of time to first clinically significant exacerbation
- Primary analysis summary Table for each study. The primary analysis will be conducted on the interim data and provide model-adjusted estimates as a supportive output.
- Summary of Subject Disposition and Reasons for Study Withdrawal
- Summary of Demographic Characteristics
- Summary of Time in Study

4.11.2.5. Decision Making

The outputs from the interim analysis will be forwarded from the SDAC to the IDMC. As the stopping rule is binding, the decision will be communicated from the SDAC to the IDMC and then to GSK following agreement from the IDMC.

4.11.3. Blinded Data Analysis for Validation Questionnaires

Blinded interim data will be used to facilitate validation of the Asthma Daily Symptom Diary/Asthma Nightly Symptom Diary (ADSD/ANSD) and PROMIS fatigue items. This blinded interim analysis will be performed when approximately 300 patients have 6 months data. No assessment of efficacy or safety will be included in this validation assessment.

This analysis is subject to a separate analysis plan held by VEO (Value Evidence & Outcomes).

4.12. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol amendment 2 (Dated: 08-APR-2022) and its rationale are summarised as below.

Substantial validation work has been conducted on the ADSD/ANSD PRO measures since the original protocol and SAP were finalised. These measures will provide additional treatment benefit information and could be included in the label for treatment decision making. Consequently, and following additional regulatory agency feedback, ADSD/ANSD change from baseline at week 52 endpoints have been added as secondary endpoints and into the hierarchy. In addition, ADSD and ANSD responders have been added as other endpoints.

5. SAMPLE SIZE DETERMINATION

Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125).

5.1. Sample Size Assumptions

A sample size of 375 participants (2:1 GSK3511294 to placebo allocation ratio) is based on sufficient power to conclude superiority on primary and key secondary endpoints.

5.1.1. Primary Endpoint

The assumed true annualised rate of exacerbations in the placebo arm is 1.18. Based on an assumed true treatment difference of a 50% reduction in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC, a sample size of 375 randomised participants (250 to GSK3511294, 125 to placebo) will provide 99% power for the primary endpoint at a 5% two-sided significance level [PASS, 2020].

The assumptions for the placebo rate and treatment effect are median values from an elicitation exercise which used Phase 3 anti-IL-5/5R historical data (~50% reduction in exacerbations) and expert opinion. The sample size is based also on an assumption of 0.8 for the dispersion parameter which was observed in two mepolizumab studies Pavord, 2012; Ortega, 2014]. It was assumed that 14% of participant-years data will be missing due to study withdrawal, which is also consistent with mepolizumab studies.

Based on the assumptions above, the minimum observed treatment difference estimated to result in significance at the 5% two-sided significance level is a 27% reduction in exacerbations for GSK3511294 + SoC compared with placebo + SoC (rate ratio of 0.73).

5.1.2. Secondary Endpoints

Table 5 describes the assumptions and power values for two key secondary endpoints. The assumptions are obtained from the Phase 3 mepolizumab studies [Pavord, 2012; Ortega, 2014; Chupp, 2017].

Table 5 Power Calculations for Key Secondary Endpoints

Endpoint	Assumed treatment difference (GSK3511294 + SoC vs. placebo + SoC)	Standard deviation	Power
Change from baseline in SGRQ total score at Week 52	-7	17	96%
Change from baseline in ACQ-5 score at Week 52	-0.35	1.1	83%

5.2. Sample Size Sensitivity

The sample size and power calculations are based on assumptions about the true values for parameters. The power of the study is dependent on changes in these assumptions, in particular the assumed annualised exacerbation rates. Table 5 illustrates how changes in assumptions for two parameters (placebo + SoC annualised exacerbation rate and treatment effect) affect the power.

Table 5 Estimates of Power for Assumed Placebo + SoC Exacerbation Rate and Assumed Percent Reduction with GSK3511294 + SoC Compared with Placebo + SoC

Percent reduction in annualised exacerbation rate with GSK3511294 + SoC vs. placebo + SoC	Placebo + SoC annualised exacerbation rate			
	1.0	1.1	**1.18**	1.3
30%	61	63	65	67
40%	88	90	91	92
50%	98	99	**99**	99

5.3. Sample Size Re-estimation or Adjustment

There will be no sample size re-estimation.

There is a possibility for randomising greater than 375 participants in the study. This is due to local country requests or requirements, for example, the local health authority specifying a minimum number to be enrolled. The primary analysis and clinical study report (CSR) will be based on the initial target enrolment. If the study target enrolment is reached before a local country enrolment requirement is met, then recruitment in that country may continue. Participants from those countries, who have already been enrolled at the time of reaching the target enrolment, will be included in the primary analysis. All data (pre- and post-target enrolment) will be analysed together but reported later in a supplement to the study report. Inferences will be drawn on the original study report based on the target enrolment.

6. SUPPORTING DOCUMENTATION

6.1. Early PK Access Key Activities

Designated representative(s) may be unblinded for performing population PK, PKPD dataset preparation and draft PK, PKPD model development using scrambled (random reassignment of subject identification numbers) PK, PKPD unblinded datasets. The PK and PKPD datasets will include information on PK concentration, actual dosing information, demographics (including race and ethnicity), vital signs, concomitant medications, antidrug antibodies, biomarkers (e.g. eosinophils and IL5 concentration) and laboratory information. No information on adverse event and efficacy will be included.

6.2. Appendix 1 Abbreviations and Trademarks

6.2.1. List of Abbreviations

Abbreviation	Description
ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
ADSD	Asthma Daily Symptom Diary
ANSD	Asthma Nightly Symptom Diary
AE	Adverse Event
AESI	Adverse Event of Special Interest
Anti-IL-5	Anti-Interleukin-5
BP	Blood pressure
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPMS	Clinical Pharmacology Modeling and Simulation
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case report form
ED	Emergency Department
eDiary	Electronic diary
FAS	Full Analysis Set
FEV1	Forced expiratory volume in 1 second
GSK	GlaxoSmithKline
HRQoL	health-related quality of life
ICS	Inhaled corticosteroids
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IL-5	Interleukin-5
LOS	Length of Stay
IM	Intramuscular
IV	Intravenous
KR method	Kenward and Roger method
LS Mean	Adjusted mean for the treatment group
LS Mean Change	Adjusted mean change from baseline for the treatment group
MAR	Missing at Random
MNAR	Missing Not at Random
Max	Maximum
MedDRA	Medicinal dictionary for regulatory activities
Min	Minimum
FAS	Full Analysis Set
Mg	Milligram
MMRM	Mixed Models Repeated Measures
NAb	Neutralising antibody
NHANES	National Health and Nutrition Examination Survey

Abbreviation	Description
OCS	Oral corticosteroids
OPS	Output and Programming Specification
OR	Odds ratio
PD	Pharmacodynamics
PEF	Peak expiratory flow
PT	Preferred Term
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PRO	Patient-reported outcomes
PROMIS	Patient-reported outcomes measurement information system
QTcF	QTc corrected by Fridericia's formula
RAP	Reporting and Analysis Plan
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SAC	Statistical Analysis Complete
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SGRQ	St George's Respiratory Questionnaire
SNOT-22	Sino-nasal Outcomes Test-22
SoC	Standard of care
SOC	System Organ Class

6.2.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

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Title Page

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Protocol Number: 213744

Compound Number: GSK3511294

Short Title: Placebo-controlled efficacy and safety study of GSK3511294 in participants with severe asthma with an eosinophilic phenotype

Sponsor Name: GlaxoSmithKline Research & Development Limited

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Version history

Table 1 SAP Version History Summary

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1	20-Jan-2021	Version 01 Approval Date: 01-OCT-2020	Not Applicable	Original version

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 213744. Details of the planned final analyses are provided.

Descriptive study population analyses such as summary of demography and baseline characteristics and additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbations[a] over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks
Other	
• To investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	• Time to first clinically significant exacerbation[a] • Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit • Change from baseline in SGRQ total score at discrete timepoints during the 52-week period

Objectives	Endpoints
	• Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period • SGRQ total score responder status at Week 52 (responder defined as achieving ≥4-point reduction from baseline) • ACQ-5 score responder status at Week 52 (responder defined as achieving ≥0.5-point reduction from baseline) • Change from baseline in Patient-Reported Outcomes Measurement Information Systems (PROMIS) Fatigue items score at discrete timepoints during the 52-week period • Change from baseline in Asthma Daily Symptom Diary (ADSD)/ Asthma Nightly Symptom Diary (ANSD) weekly mean score at specified timepoints during the 52-week period • Change from baseline in awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean • Change from baseline in morning peak expiratory flow (PEF) 2-week mean • Change from baseline in daily asthma symptom scores 2-week mean • Change from baseline in mean number of occasions of rescue medication use/day 2-week mean • Mean number of days with oral corticosteroids (OCS) usage over 52 weeks • Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period • Change from baseline in Sino-nasal Outcomes Test-22 (SNOT-22) score at discrete timepoints during the 52-week period
• To investigate GSK3511294 versus placebo on top of existing asthma therapy on	• Patient-rated response to therapy at discrete timepoints during the 52-week period

Objectives	Endpoints
• patient- and clinician-rated response to therapy • patient global impression of asthma severity and its change from baseline	• Clinician-rated response to therapy at discrete timepoints during the 52-week period • Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period • Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during the 52-week period
• To investigate the PD effects of GSK3511294	• Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period
• To investigate the PK of GSK3511294	• GSK3511294 plasma concentration at discrete timepoints during the 52-week period
Safety	
• To evaluate the safety and tolerability of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Incidence of AEs/SAEs • Laboratory parameters, including haematological and clinical chemistry parameters • Vital signs including blood pressure (BP), body temperature, and pulse rate • ECG assessments • Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294
Health Resource Use	
• To further evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on healthcare utilisation on top of existing asthma therapy	• Healthcare utilisation for asthma including hospitalisation, ED, and physician office/clinic visits

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit. For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

1.1.2. Estimands

Table 2 Estimands

The following two attributes apply to all estimands:

- Treatment comparison: GSK3511294 + SoC compared with placebo + SoC
- Population: Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Objectives	**Estimand**		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
Primary objective: To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	Annualised rate of clinically significant exacerbations over 52 weeks	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred • Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2): treatment policy strategy i.e.	Ratio of the rates of exacerbations between GSK3511294 + SoC and placebo + SoC.

Objectives	**Estimand**		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		regardless of the intercurrent event occurring	
Secondary objective: to evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	a) Change from baseline in SGRQ total score at Week 52 b) Change from baseline in ACQ-5 score at Week 52 c) Change from baseline in pre-bronchodilator FEV_1 at Week 52 l) Annualised rate of clinically significant exacerbations requiring hospitalisation	• Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be handled with a hypothetical strategy i.e. had the intercurrent event not occurred • Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2): to be handled with a treatment policy i.e. regardless of the intercurrent event occurring	a) Difference in mean change from baseline in SGRQ total score at Week 52 between GSK3511294 + SoC and placebo + SoC b) Difference in mean change from baseline in ACQ-5 score at Week 52 between GSK3511294 + SoC and placebo + SoC c) Difference in mean change from baseline in pre-bronchodilator FEV_1 at Week 52 between GSK3511294 + SoC and placebo + SoC d) Ratio of the rates of clinically significant exacerbations requiring hospitalisation and/or ED visit between

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	and/or ED visit over 52 weeks		GSK3511294 + SoC and placebo + SoC
Other objective: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	a) Time to first clinically significant exacerbation b) Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit c) Change from baseline in SGRQ total score at discrete timepoints during the 52-week period d) Change from baseline in ACQ-5 score at discrete	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred • Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring	a) Hazard ratio of first clinically significant exacerbation between GSK3511294 + SoC and placebo + SoC b) Hazard ratio of first clinically significant exacerbation requiring hospitalisation and/or ED visit between GSK3511294 + SoC and placebo + SoC c) Difference in mean change from baseline in SGRQ total score at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC d) Difference in mean change from baseline in ACQ-5 score at discrete timepoints during

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	timepoints during the 52-week period e) Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period f) Change from baseline in Sino-nasal Outcomes Test-22 (SNOT-22) score at discrete timepoints during the 52-week period g) Change from baseline in ADSD/ANSD weekly mean score at specified timepoints during the 52-week period		the 52-week period between GSK3511294 + SoC and placebo + SoC e) Difference in mean change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC f) Difference in mean change from baseline SNOT-22 score at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC g) Difference in mean change from baseline in ADSD/ ANSD weekly mean score

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
			between GSK3511294 + SoC and placebo + SoC
• **Other objective**: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	a) SGRQ total score responder status at Week 52 (responder defined as achieving ≥4-point reduction from baseline) b) ACQ-5 score responder status at Week 52 (responder defined as achieving ≥0.5-point reduction from baseline)	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred. Status following IE will be set as missing. • Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring	a) Odds ratio in SGRQ total score responder status at Week 52 between GSK3511294 + SoC and placebo + SoC b) Odds ratio in ACQ-5 score responder status at Week 52 between GSK3511294 + SoC and placebo + SoC

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
• **Other objective**: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	a) Change from baseline in PROMIS Fatigue items score at discrete timepoints during the 52-week period b) Change from baseline in awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean c) Change from baseline in morning peak expiratory flow (PEF) 2-week mean d) Change from baseline in daily asthma symptom scores 2-week mean	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data.	a) Descriptive summary of change from baseline in PROMIS Fatigue items score by treatment group and by visit b) Descriptive summary of change from baseline in 2-weekly mean awakenings at night due to asthma symptoms requiring rescue medication use by treatment group and by time interval c) Descriptive summary of change from baseline in 2-week mean morning PEF by treatment group and by time interval d) Descriptive summary of change from baseline in daily asthma symptom scores 2-

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	e) Change from baseline in mean number of occasions of rescue medication use/day 2 week mean f) Mean number of days with oral corticosteroids (OCS) usage over 52 weeks		week mean by treatment group and by time interval e) Descriptive summary of change from baseline in 2 week mean number of occasions of rescue medication use/day by treatment group and by visit and time interval f) Descriptive summary of mean number of days OCS usage over 52 weeks by treatment group
Other objective: to investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient- and clinician-rated response to therapy	• Patient-rated response to therapy at discrete timepoints during the 52-week period • Clinician-rated response to therapy at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: while on	Descriptive summary of (by treatment group) • Patient-rated response to therapy at discrete timepoints during the 52-week period • Clinician-rated response to therapy at discrete timepoints during the 52-week period

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data.	
Other objective: to investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient global impression of asthma severity and its change from baseline	• Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period • Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred	Odds ratio in • PGI-S of asthma at discrete timepoints during the 52-week period • PGI-C from baseline of asthma severity at discrete timepoints during the 52-week period

Objectives	**Estimand**		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		• Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring	
Other objective: to investigate the PD effects of GSK3511294	Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: while on treatment strategy i.e. only data collected while participant was on-treatment will be used on the analysis. Blood eosinophil counts taken more than 26 weeks following last dose will not be included in the analysis. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: same as above • Change in maintenance therapy or use of prohibited medications (listed in protocol Section	ratio in absolute blood eosinophil count GSK3511294 + SoC vs. placebo + SoC

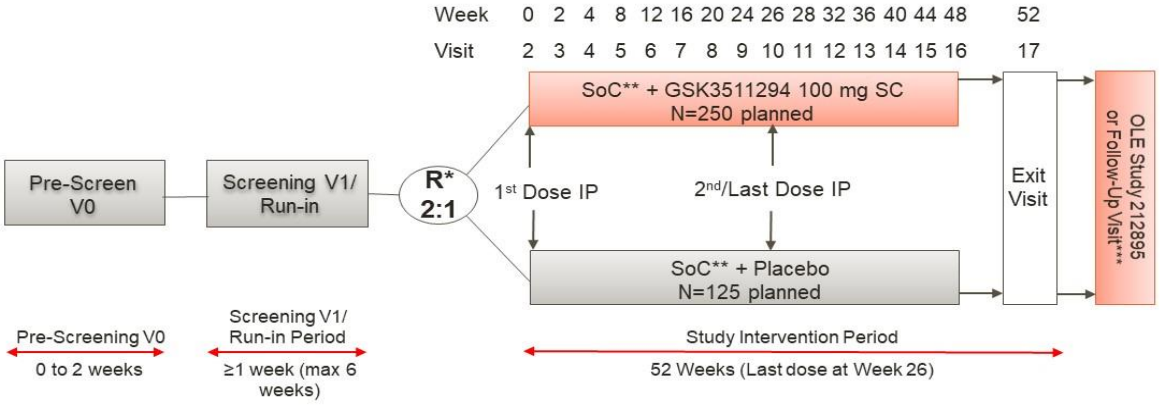
Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		6.9.2):hypothetical strategy, i.e.had the intercurrent event not occurred. •	
Other objective: to investigate the PK of GSK3511294	GSK3511294 plasma concentration at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2): hypothetical strategy, i.e.had the intercurrent event not occurred.	Descriptive summarise of GSK3511294 plasma concentration by visit. (GSK3511294 + SoC arm only)

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
Safety objective: To evaluate the safety and tolerability of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	a) Incidence of AEs/SAEs b) Laboratory parameters, including haematological and clinical chemistry parameters c) Vital signs including blood pressure (BP), body temperature, and pulse rate d) ECG assessments e) Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Change in maintenance therapy or use of prohibited medications (listed in protocol Section 6.9.2): treatment policy strategy i.e. regardless of the intercurrent event occurring	Descriptive summaries of a) Incidence of AEs/SAEs b) Laboratory parameters, including haematological and clinical chemistry parameters c) Vital signs including blood pressure (BP), body temperature, and pulse rate d) ECG assessments e) Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294

Objectives	**Estimand**		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
Health Resource Use: To further evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on healthcare utilisation on top of existing asthma therapy	Healthcare utilisation for asthma including hospitalisation (including ICU admissions and Length of Stay-LOS), ED, and physician office/clinic visits (scheduled and unscheduled)	Same strategy as per primary endpoint	Descriptive summarise of healthcare utilisation

1.2. Study Design

Overview of Study Design and Key Features



** R = Randomisation: To be randomised participants without a historical blood eosinophil count of ≥300 cells/µL must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. Participants will remain on their standard of care (SoC) asthma therapy throughout the intervention period and will be randomised 2:1 to receive GSK3511294 (100 mg) or placebo.*
*** SoC = medium to high dose ICS (≥440 µg FP HFA daily or clinical comparability) plus additional controller. SoC asthma therapy to exclude biologics.*
**** OLE = Open label extension. Willing participants will continue directly into OLE Study 212895. Participants unwilling to continue will have a follow-up visit 4 weeks after the Exit Visit.*

Design Features	• Phase 3A • 52-week treatment period • Randomised • Double-blind • Placebo-controlled • Parallel group • Multi-centre • Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125). • A sample size of 375 randomised will provide 99% power to demonstrate superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC in annualised rate of clinically significant exacerbations over 52 weeks, based on the true annualised rate of exacerbations in the placebo arm being 1.18 , an assumed true treatment difference of a 50% reduction and at a 5% two-sided significance level. • Participants who receive both doses of study intervention and complete the Exit Visit will be eligible to participate in an open-label extension (OLE) study (Study 212895), during which they will receive two doses of open-label GSK3511294 100 mg SC over another 52 weeks.
Study intervention and Study intervention Assignment	The study will consist of a pre-screen period (0-2 weeks), a run-in period (1-6 weeks), and a study intervention period (52 weeks). After the run-in period, participants will be randomised in a 2:1 ratio using an interactive response technology (IRT) system in a blinded manner to receive either GSK3511294 100 mg or placebo by SC injection. Randomisation will be stratified based on baseline ICS dose (medium or high dose). Two doses of study intervention will be administered in the clinic: the first at randomisation Visit 2 (Week 0) and the second at Visit 10 (Week 26). Participants will be assessed at each scheduled visit (a total of 17 study visits) during the 52-week

Overview of Study Design and Key Features	
	treatment phase. Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 10, Exit Visit 17, and WS Visit (if applicable). Participants will remain on their existing stable maintenance asthma therapy throughout the study.
Interim Analysis	• No interim analyses of efficacy data are planned. • IDMC review of safety data is planned.

2. STATISTICAL HYPOTHESES

The primary study objective is to test for the superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC, assessed by the annualised rate of clinically significant exacerbations measured over the study intervention period of 52 weeks.

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 and placebo.

2.1. Multiplicity Adjustment

The treatment comparison of interest for the primary and secondary endpoints is GSK3511294 100 mg SC + SoC vs placebo + SoC. A fixed sequence hierarchical testing procedure will be used to provide strong control of Type I error for multiplicity arising from the primary and multiple secondary endpoints. This will be carried out using a stepdown closed testing procedure where inference for an endpoint in the predefined hierarchy will be dependent on statistical significance having been achieved for the previous endpoints in the hierarchy. For example, for the primary endpoint, GSK3511294 + SoC will be compared to placebo + SoC at a two-sided 5% level. The next endpoint in the hierarchy (i.e. the first secondary endpoint) will be tested only if the test for the primary endpoint is significant at the two-sided 5% level. Testing will continue down the hierarchy for the remaining endpoints in an equivalent manner only if the previous endpoint in the hierarchy achieves statistical significance.

The hierarchy of the primary and secondary endpoints to be tested is as follows:

1. Annualised rate of clinically significant exacerbations over 52 weeks

2. Change from baseline in SGRQ at Week 52

3. Change from baseline in ACQ-5 at Week 52

4. Change from baseline in clinic pre-bronchodilator FEV_1 at Week 52

5. Annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled	All participants who sign the ICF and for whom a record exists.	Study Population
Modified Intent-to-Treat (mITT)	All randomised participants who receive at least one dose of study intervention. This population will serve as the primary population for analyses of study population, efficacy, safety, immunogenicity, PD and health resource use endpoints. Data will be analysed according to randomised treatment arm.	• Study Population • Efficacy • Safety • Immunogenicity • PD • Health Resource Use
mITT-PROMIS	All participants in the mITT population for whom at least one PROMIS fatigue items were administered	• Efficacy (PROMIS)
mITT-SNOT-22	All participants in the mITT population for whom at least one SNOT-22 questionnaire were administered	• Efficacy (SNOT-22)
PK	All participants in the mITT population for whom at least one pharmacokinetic sample was obtained, analysed and was measurable.	• PK

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The Modified Intent-to-Treat (mITT) Analysis Set will be used for all Study Population, Efficacy, Safety, Immunogenicity and PD analyses, unless otherwise stated. The Output and Programming Specification (OPS) document will provide more details.

Confidence intervals will use 95% confidence intervals (CI) unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

For endpoints that are formally modelled, summary statistics will be provided.

Where statistical models are used, if there are important departures from the distributional assumptions, transformations of covariates or alternative models may be explored as supporting analyses.

Randomisation is stratified based on baseline ICS dose (medium or high). All statistical models will include this stratum as a covariate. In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the data collected in the CRF, not the assigned stratum at randomization.

Assessments collected at withdrawal visit will be included in summary tables but won't be included in any statistical analysis.

4.1.2. Baseline Definition

Baseline values for visit based assessments and eDiary assessments are defined in Table 3.

In general, the baseline values for visit based assessment will be the Visit 2 pre-dose assessment. If a value is missing at visit 2 then the value recorded at visit 1 (screening) will be used as the baseline.

Unless otherwise stated, if baseline is missing no derivation will be performed and baseline will be set to missing.

Table 3 Baseline Definitions & Derivations

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
Efficacy, Health Outcomes and Other			
SGRQ total and domain scores		X	Day 1 pre-dose
ACQ-5		X	Day 1 pre-dose
Pre-bronchodilator FEV_1	X	X	Day 1 pre-dose
Post-bronchodilator FEV_1	X	X	Day 1 pre-dose
PROMIS Fatigue items score		X	Day 1 pre-dose
ADSD/ANSD weekly mean score	X (daily following Screening)		Average of measurements from Day -7 to Day 1 inclusive (at least 4 days must be non-missing)

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean	X (daily following Screening)		Average of measurements from Day -7 to Day 1 inclusive (at least 4 days must be non-missing)
morning PEF 2-week mean	X (daily following Screening)		Average of measurements from Day -7 to Day 1 inclusive (at least 4 days must be non-missing)
daily asthma symptom scores 2-week mean	X (daily following Screening)		Average of measurements from Day -7 to Day 1 inclusive (at least 4 days must be non-missing)
mean number of occasions of rescue medication use/day 2-week mean	X (daily following Screening)		Average of measurements from Day -7 to Day 1 inclusive (at least 4 days must be non-missing)
SNOT-22 score		X	Day 1 pre-dose
PGI-S	X	X	Day 1 pre-dose
Safety			
Blood pressure	X	X	Values from most recent assessment prior to first dose of study treatment which records both systolic and diastolic BP
Pulse rate	X	X	Most recent individual value prior to first dose of study treatment
Clinical Chemistry	X	X	Most recent individual value prior to first dose of study treatment
ECG endpoints	X	X	Values from most recent ECG conducted prior to first dose of study treatment
Hematology with differential (including eosinophil count)	X	X	Most recent individual value prior to first dose of study treatment
Other			
Complement C3 and C4		X	Day 1 pre-dose
Immunogenicity		X	Day 1 pre-dose

NOTES :

- Only records that have been assigned a treatment phase of 'pre-treatment' will be considered as baseline assessments.
- Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

4.1.3. Multicenter Studies

For the purposes of covariate adjustment in the statistical analysis, countries will be grouped into regions. The following regions are defined:

- European (Czechia, France, Italy, Poland, Spain)
- US
- Rest of World (Canada, Japan)

If there are insufficient subjects in each region for the statistical procedures to converge satisfactorily, the combining of regions will be considered.

4.2. Primary Endpoint Analyses

4.2.1. Definition of endpoint

The primary endpoint is the annualized rate of clinically significant exacerbations over the 52 weeks following randomisation.

Clinically significant exacerbations of asthma are defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see protocol Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

Exacerbations recorded in the eCRF are considered as verified clinically significant exacerbations and will be included in the primary analysis.

Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

4.2.2. Main analytical approach

Primary Statistical Analyses
Endpoint(s)
• Annualized rate of clinically significant exacerbations over 52 weeks
Model Specification
• Generalized linear model assuming a negative binomial distribution • Terms in the model:

Primary Statistical Analyses
• **Response**: number of recorded clinically significant exacerbations experienced per subject. • **Categorical**: treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbation history (as an ordinal variable (2, 3, 4+)), baseline ICS dose (medium, high), geographical region • **Continuous**: baseline pre-bronchodilator % predicted FEV_1 • **Offset**: Log_e(total time in the study in years)
Model Checking & Diagnostics
• The fit of the regression models will be examined using "Q-Q" plots of the standardized residuals. Interpretation of these plots will be aided by the addition of simulation-generated tolerance boundaries.
Results Presentation
• Treatment group model estimated annualized exacerbation rates and associated 95% CI • pairwise treatment rate ratios and associated p-value and 95% CI. • pairwise treatment percent reductions in annual exacerbation rate and associated 95% CI
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed "missing at random" (MAR) (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the primary endpoint, the data for the period following withdrawal will be assumed MAR (based on all data included in the analysis under the current estimand strategy).
Subgroup Analysis
• By baseline ICS dose (medium, high) subgroup analysis will be performed.

4.2.3. Sensitivity analyses

For the main analytical approach, data that is missing due to study withdrawal is assumed to be missing at random. The aim of sensitivity analyses is to assess the robustness in the treatment effect and conclusion in the main analytical approach when departing from the missing at random assumption. Two sensitivity analyses will be performed to for this investigation.

4.2.3.1. Sensitivity Analysis 1 (MNAR Based on off-treatment Data)

This sensitivity analysis will be performed where subjects who withdrew from the study early will have missing data imputed for the period of time between withdrawal from the study to the Week 52 visit based on the off-treatment data collected from subjects who continued in the study following discontinuation of randomised intervention. Multiple imputation methods will be used with results combined across imputations using Rubin's method [Roger, 2018].

If the total unobserved/excluded time in the study is <3% of the total study duration or if <50% of the total off-treatment period is observed then the sensitivity analysis will not be conducted.

4.2.3.2. Sensitivity Analysis 2 (Tipping Point Analysis)

Tipping point analysis will explore the impact of missing data by using differing assumptions regarding the exacerbation rate in subjects who withdraw from the study. Subjects who withdrew from study early will have missing data imputed for the period of time between withdrawal from the study to the Week 52 visit based on a range of values for the rate of exacerbations per year following study withdrawal. The values to be investigated will be based on increases relative to the estimated rates obtained within each arm under the MAR assumption. The imputed exacerbation rates will vary independently for the active and placebo arms, and will include scenarios where subjects in the active arm have worse outcomes following early withdrawal from the study than subjects in the placebo arm. The tipping point multiple imputation method will be based on pattern mixture models [Keene, 2014]. The results from the analyses of each sample are combined using Rubin's method.

If the total unobserved/excluded time in the study is <3% of the total study duration or if <50% of the total off-treatment period is observed then the sensitivity analysis will not be conducted.

4.3. Secondary Endpoints Analyses

4.3.1. Definition of endpoint(s)

The secondary endpoints are:

- Change from baseline in SGRQ total score at Week 52
- Change from baseline in ACQ-5 score at Week 52
- Change from baseline in pre-bronchodilator FEV_1 at Week 52
- Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks

4.3.2. Main analytical approach for SGRQ total score, ACQ-5 score and pre-bronchodilator FEV_1

Secondary Endpoints Analyses
Endpoint(s)
• Change from baseline in SGRQ total score at Week 52 • Change from baseline in ACQ-5 score at Week 52 • Change from baseline in pre-bronchodilator FEV_1 at Week 52
Model Specification
• Mixed Models Repeated Measures (MMRM) model. • Terms in the model: **Response:** SGRQ Total score or ACQ-5 score or pre-bronchodilator FEV1 at each visit. **Categorical:** treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high), exacerbation history (as an ordinal variable (2, 3, 4+)), geographical region, visit **Continuous**: baseline (SGRQ Total score, or ACQ-5 score, baseline pre-bronchodilator % predicted FEV1 **Interaction:** baseline*visit, treatment group*visit **Repeated:** visit

Secondary Endpoints Analyses
• The MMRM analysis for SGRQ total scores will include data collected at Weeks 4, 12, 26, 40 and 52. The MMRM analysis for ACQ-5 score will include data collected at Weeks 2, 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48 and 52. The MMRM analysis for pre-bronchodilator FEV1 will include data collected at Weeks 26 and 52. • The model will be fit with an unstructured variance-covariance matrix. • The Kenward and Roger method (KR) for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. In the event the model fails to run using the KR method, then the residual method will be used instead. In the event the model fails to run using residual method and assessments are from many timepoints, timepoints included in the analysis may be reduced by keeping the timepoints/intervals of most interest. • Baseline is defined in Section 4.1.2 • Two models will be fitted; one with a response variable of change from baseline and one with the response variable as the raw value.
Model Checking & Diagnostics
• The fit of the regression models will be examined using "Q-Q" plots of the standardized residuals. Interpretation of these plots will be aided by the addition of simulation-generated tolerance boundaries.
Results Presentation
• Least-square (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI and P-values for each visit will be presented. • The LS mean treatment differences (and associated 95% CIs) for all visits will also be presented graphically. • SGRQ total scores, ACQ-5 score and pre-bronchodilator FEV1 (absolute value and changes from baseline) will also be summarised by treatment group and visit.
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.3.3. Main analytical approach for annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

The annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks will be analysed using a negative binomial generalised linear model, as described for the primary endpoint, Section 4.2.2 for details.

4.3.4. Sensitivity analyses

The sensitivity analyses for the primary endpoint as described in Section 4.2.3 will also be performed for the secondary endpoints.

4.4. Other Endpoints Analyses

4.4.1. Time to first clinically significant exacerbation and Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit

Other Endpoints Analyses
Endpoint(s)
• Time to first clinically significant exacerbation • Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit
Model Specification
• Cox's proportional hazards model • Terms in the model: **Response**: time to first clinically significant exacerbation or first clinically significant exacerbation requiring hospitalization and/or ED visit **Categorical**: treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbation history (as an ordinal variable (2, 3, 4+)), baseline ICS dose (medium, high), geographical region **Continuous**: baseline pre-bronchodilator % predicted FEV1 • The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead. • Kaplan-Meier survivor functions will be obtained for each treatment group using PROC LIFETEST with a TIME statement.
Model Checking & Diagnostics
• The proportional hazards assumption will be examined by obtaining the Kaplan-Meier estimates of the survival function S(t) over time separately for each treatment group. In addition, the ln {-ln[S(t)]} plot will be produced.
Results Presentation
• Hazard ratios and the percent reduction in risk for the pairwise treatment comparisons with associated 95% CIs and p-values will be presented. • The Kaplan-Meier curves will be presented showing the probability of having an event over time for each treatment group separately plotted on the same figure.
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.2. Change from baseline in SGRQ total score and in ACQ-5 score at discrete timepoints during the 52-week period

Analytic approach for change from baseline in SGRQ total score and change from baseline in ACQ-5 score at discrete timepoints during the 52-week period has been included in the secondary endpoints analyse, see Section 4.3.2 for details.

4.4.3. SGRQ total score responder status at Week 52 and ACQ-5 score responder status at Week 52

Other Endpoints Analyses
Endpoint(s)
• Proportion of responders according to SGRQ total score (responder defined as achieving ≥4-point reduction from baseline) • Proportion of responders according to ACQ-5 score (responder defined as achieving ≥0.5-point reduction from baseline)
Model Specification
Generalized linear mixed model • Terms in the model: **Dependent:** response (yes/no) **Categorical:** treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high), exacerbation history (as an ordinal variable (2, 3, 4+)), geographical region, visit, subject **Continuous**: baseline (SGRQ Total score, or ACQ-5 score), baseline pre-bronchodilator % predicted FEV1 **Interaction:** baseline (SGRQ Total score, or ACQ-5 score)*visit, treatment group*visit The model will be fit with an unstructured variance-covariance matrix with one single model to include all visits where the assessment in question is scheduled to be performed. • Computation of confidence intervals for the odds ratios is based on the individual Wald tests. • The analysis of responder based on SGRQ total scores will include data collected at Weeks 4, 12, 26, 40 and 52. The analysis of responder based on ACQ-5 score will include data collected at Weeks 2, 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48 and 52. • In the event the model fails to run and assessments are from many timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest.
Model Checking & Diagnostics
• Pearson residuals will be plotted by using PLOTS=PEARSONPANEL option for the model statement in SAS.
Results Presentation
• Number and percentage of responders and non-responders for each treatment at each visit • Odds ratio for pairwise comparisons with associated 95 % CIs and p-values
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy).

• For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.4. Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1

Analytic approach for change from baseline in pre-bronchodilator FEV_1 at discrete timepoints during the 52-week period has been included in the secondary endpoint analysis of change from baseline in pre-bronchodilator FEV_1 at Week 52, see Section 4.3.2 for details.

Change from baseline in post-bronchodilator FEV_1 at discrete timepoints during the 52-week period will be analyzed in the same approach as for change from baseline in pre-bronchodilator FEV_1.

4.4.5. PROMIS Fatigue items score

PROMIS Fatigue items score and change from baseline in PROMIS Fatigue items score will be summaried by treatment group and visit.

4.4.6. SNOT-22 score

The SNOT-22 questionnaire is administered (post randomisation) at Week 26 and 52. The 22 questions of the SNOT-22 are each graded on a 6-point scale ranging from 0 = 'no symptoms' to 5 = 'as bad as things could be'. The scores for each of the questions are summed to derive the total score which ranges from 0 to 110, with higher scores representing worse quality of life.

Other Endpoints Analyses
Endpoint(s)
• Change from baseline in SNOT-22 total score at Week 26 and Week 52
Model Specification, Model Checking & Diagnostics
• See Model Specification, Model Checking & Diagnostics for secondary endpoints statistical analyses • analysis will include data collected at Weeks 26 and 52.
Model Results Presentation
• See Model Results Presentation for secondary endpoints statistical analyses (figures will not be presented) • SNOT-22 score (absolute value and changes from baseline) will also be summarised by treatment group and visit.
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy).

- For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.7. Patient-rated response to therapy during the 52-week period

This is an overall evaluation of response to treatment, conducted by the participant at Week 12, 26, 40 and 52 using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse

Patients rated response to therapy will be summarised by treatment group and visit.

4.4.8. Clinician-rated response to therapy during the 52-week period

This is an overall evaluation of response to treatment, conducted by the investigator at Week 12, 26, 40 and 52 using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse

Clinician rated response to therapy will be summarised by treatment group and visit.

4.4.9. Patient Global Impression of Asthma Severity/Change (PGI-S, PGI-C)

Patient Global Impression of Asthma Severity (PGI-S): The participant will complete a PGI-S question at the visits: Randomisation and Screening, Day 1, Week 12, 20, 26, 40, 52. This single global question will ask participants to rate their asthma severity on a five-point scale (no symptoms, mild, moderate, severe, very severe). Responses will be captured electronically.

Patient Global Impression of Change (PGI-C) from Baseline of Asthma Severity: The participant will complete a PGI-C question from baseline of their asthma severity at Week 12, 20, 26, 40 and 52. The single question will ask participants to rate the overall

change in their asthma severity compared with Day 1 (randomisation) prior to start of study intervention. The rating will use a five-point scale (much better, a little better, no change, a little worse, much worse) and responses will be captured electronically.

Other Endpoints Analyses
Endpoint(s)
• Patient global impression of asthma severity (PGI-S) • Patient global impression of change (PGI-C) from baseline of asthma severity
Model Specification
• Ordinal Logistic regression model (proportional odds model) • Terms in the model: Dependent: response (5-point scale) Categorical: treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), baseline ICS dose (medium or high), exacerbation history (as an ordinal variable (2, 3, 4+)), geographical region Continuous: baseline pre-bronchodilator % predicted FEV1 • The model will be fit at each visit (Weeks 12, 20, 26, 40 and 52). • Subjects with a missing response at a particular visit will be included in the "Significantly Worse" category in the ordinal logistic regression model for the analysis of that visit. • Inference will primarily be based on the Week 24 comparison.
Model Checking & Diagnostics
• The proportional hazards assumption will be examined by obtaining the Kaplan-Meier estimates of the survival function S(t) over time separately for each treatment group. In addition, the ln {-ln[S(t)]} plot will be produced.
Results Presentation
• The number and percentage of subjects in each response category and with a missing response summarised by treatment group for each visit. • The estimated odds ratio for the treatment variable in the ordinal logistic regression model and corresponding 95% CI and p-value
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.10. ADSD/ANSD (and responder based on ADSD/ANSD)

The ADSD/ANSD is a 6-item self-administered patient-reported diary developed by the PRO Consortium's Asthma Working Group (in accordance with the Food and Drug Administration's PRO Guidance) to facilitate comprehensive and reliable assessment of asthma symptoms from a patient's perspective which received qualification from the FDA in March 2019 supporting use in drug development as an exploratory measure.

The ADSD/ANSD is intended for use by adults and adolescents (aged 12 years and older) who are diagnosed with asthma to rate the severity of their symptoms in the three core categories: breathing symptoms (wheezing, shortness of breath), chest symptoms (chest tightness, chest pain) and cough.

The ADSD/ANSD must be completed twice daily by the participant daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.:

- The morning diary (ADSD) is to be completed upon waking and refers to asthma symptoms during the night-time.
- The evening diary (ANSD) is to be completed before going to bed and refers to asthma symptoms during the day.

Participants are required to rate the six symptoms at their worst during the respective timeframes using an 11-point numeric rating scale (NRS) ranging from 0 ('None') to 10 ('As bad as you can imagine'). Responses will be captured electronically.

To date no definition of meaningful within-patient change has been published. GSK studies 214135 and 214566 will complete prior to LSLV in this study and will provide this definition of response required to interpret change from baseline and to be used in responder analysis. Therefore, details of responder analysis will be subject to a SAP amendment (or a supplementary SAP) at a later stage.

Other Endpoints Analyses
Endpoint(s)
• Change from baseline in Asthma Daily Symptom Diary (ADSD) weekly mean score at timepoints during the 52-week period (weekly up to Week 16 and then every visit) • Change from baseline in Asthma Nightly Symptom Diary (ANSD) weekly mean score at timepoints during the 52-week period (weekly up to Week 16 and then every visit)
Model Specification, Model Checking & Diagnostics
• Similar to model specification, model checking and diagnostics detailed in Section 4.3.2 • Response variable: weekly mean scores • Baseline score is defined in Section 4.1.2
Model Results Presentation
• LS means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI and P-values for each Week will be presented. • The LS mean treatment differences (and associated 95% CIs) for all weeks will also be presented graphically. • ADSD and ANSD weekly mean absolute score and changes from baseline will also be summarised by treatment group and visit. Summary will include weekly mean score at all visits (including all weeks prior to week 16). .
Handling of missing data and data excluded due to intercurrent events
• Same approach as described in Section 4.3.2

4.4.11. Mean number of occasions of rescue medication per day

Daily diary data for rescue medication (salbutamol/albuterol) use will be aggregated over 2-week periods, then the mean daily usage, excluding days with missing data, will be calculated for each 2-week period (Weeks 1-2, 3-4,…, 51-52). Data for each 2-week period, and change from baseline for each 2-week period will be summarised by treatment group and visit. For definition of baseline see Section 4.1.2.

4.4.12. Awakenings at night due to asthma symptoms requiring rescue medication use

Awakening at night due to asthma symptoms requiring rescue medication use will be summarised as for rescue medication use, see Section 4.4.11.

4.4.13. Morning peak expiratory flow (PEF)

Morning PEF will be summarised as for rescue medication use, see Section 4.4.11.

The summaries will be for :

1) all data included as per mITT population

2) excluding data where asthma medication was taken up to 6 hours prior to PEF assessment

4.4.14. Daily asthma symptom scores

Daily asthma symptom score will be summarised as for rescue medication use, see Section 4.4.11.

4.4.15. Number of days with oral corticosteroids

Total number of days of oral corticosteroids (OCS) use over 52 weeks that are associated with clinically significant exacerbations per subject will be summarised by treatment group. Also, number of clinically significant exacerbations, number of clinically significant exacerbations treated with OCS, and mean number of days using OCS per clinically significant exacerbations treated with OCS will be summarised by treatment group.

Number of subjects on maintenance OCS at screening, total number of days of maintenance OCS use over 52 weeks and mean number of days of maintenance OCS use per subject will also be summarised by treatment group.

4.5. CLINICAL PHARMACOLOGY DATA ANALYSES

4.5.1. Pharmacokinetic Analyses

In this study, GSK3511294 plasma concentration are collected at discrete timepoints during the 52-week treatment period. GSK3511294 plasma concentration will be summarised by visit. (GSK3511294 + SoC arm only).

The PK data from this study will be included in a meta-analysis of the PK and PKPD data across all GSK3511294 studies. Details of meta-analysis will be in a separate CPMS RAP.

4.5.2. Pharmacodynamic Analyses - Blood Eosinophils

Blood eosinophil counts will be loge-transformed prior to analysis. Non-detectable blood eosinophil values of 0 GI/L, or results below the limit of quantification will be imputed by half of the lowest observed detectable (non-zero) value in the study dataset, prior to log transformation.

Ratio to baseline during W52 will be analysed using a MMRM analysis. Model specification, model checking and diagnostics are the same as described for secondary endpoints statistical analyses, see Section 4.3.1. Analysis will include data from all visits that blood eosinophils data is collected. LS Mean (SE) and LS Mean ratio to screening (SE) in each treatment group will be presented. Mean treatment ratio and 95% CI for GSK3511294 vs placebo will also be presented.

Absolute and ratio to baseline blood eosinophil counts will be summarised by treatment group and visit. Only results from the central laboratory will be included in the summary, however all data will be listed.

4.6. Safety Analyses

All safety analyses will be performed on the mITT Analysis Set. Data will be analysed according to randomised treatment arm except for the very unlikely case that participant has taken all treatments differed to randomised treatment. In this case, the actual treatment for this participant will be used in the analysis. Summaries of data will report data according to the nominal visit for which it was recorded. Occurrence of Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESIs), laboratory data, vital signs, and ECGs will be included in data displays in the form of listings, frequency tables, summary statistics, graphs, and statistical analyses where appropriate. In addition, a listing of AEs will be produced for all participants who received at least once other than randomised treatment during the study

4.6.1. Extent of Exposure

Two doses of study treatment will be administered during study treatment period: the first at randomisation Visit 2 (Week 0) and the second at Visit 10 (Week 26). Each dose is viewed as providing therapeutic coverage for 26 weeks (182 days). The number of treatments administered and the number of days exposure will be summarised descriptively and listed. Total subject-year exposure will also be presented.

Number of days of exposure to study treatment will be calculated as follow:
Duration of Exposure in Days = (Date of Final Dose) – (Date of First Dose) + 182

Subject years exposure is calculated as follow:

Subject Years Exposure = ((Date of Final Dose) – (Date of First Dose) + 182)/365.25

The exposure summary will also be presented by age subgroup (12-17, 18-64, ≥65).

4.6.2. Adverse Events

Adverse events analyses including the analysis of adverse events (AEs), Serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards.

An overview summary of AEs, including counts and percentages of participants with any AE, AEs related to study intervention, AEs leading to permanent discontinuation of study intervention or withdrawal from study, study intervention related AEs leading to permanent discontinuation of study intervention or withdrawal from study, SAEs, SAEs related to study intervention, fatal SAEs, and fatal SAEs related to study intervention will be produced. These summaries will also be produced by age subgroup (12-17, 18-64, ≥65).

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

The frequency and percentage of AEs will be summarized in two ways: 1) in descending order by System Organ Class (SOC) and Preferred Term (PT). 2) in descending order by PT only.

A separate summary will be provided for study intervention-related AEs. A study intervention-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as “Yes”. A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study intervention as ‘Yes’ or missing. The summary table will be displayed in descending order by SOC and PT.

All SAEs will be tabulated based on the number and percentage of participants who experienced the event. Separate summaries will also be provided for study intervention-related SAEs. The summary tables will be displayed in descending order by SOC and PT.

A study intervention-related SAE is defined as an SAE for which the investigator classifies the relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study intervention as 'Yes' or missing. The summary table will be displayed in descending order by SOC and PT.

4.6.2.1. Adverse Events of Special Interest

Adverse events of special interest (AESI) for GSK3511294 program include:

- Allergic reactions including anaphylaxis

  Note: these events will be assessed by the investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis.

- Type III hypersensitivity (immune complex disease/vasculitis) reactions
- Local injection site reactions
- QTc prolongation

AESI reported by the investigator as systemic reactions (further categorised by the investigator as either allergic [type I hypersensitivity] or other systemic reactions and assessed against Sampson criteria for anaphylaxis) are collected via targeted eCRF within the study. Vasculitis events and local injection site reactions are also collected via targeted eCRF within the study.

Separate summary tables showing the number and percent of subjects with each type of AESI (excluding QTc prolongation) broken down by preferred term will be created.

For each type of AESI (excluding QTc prolongation) a profile summary table will be produced containing information including, but not limited to, the number of occurrences of the event, event characteristics, time to onset, intensity, outcome and action taken.

A summary of the incidence of serious adverse events and adverse events of special interest (excluding QTc prolongation) will be produced displaying the relative risk and risk difference and their 95% CIs between and GSK3511294 and placebo.

AESI of QTc prolongation will be summarised as detailed in Section 4.6.3.3 ECG.

Separate listings of AESIs identified by the investigator as anaphylaxis, allergic (type I hypersensitivity), other systemic reactions, vasculitis events and local injection site reactions will be produced. Patient profile of on treatment adverse events of vasculitis will also be listed.

4.6.3. Additional Safety Assessments

4.6.3.1. Laboratory Data

Summaries of laboratory data including chemistry and haematology parameters, and liver chemistry test data will be based on GSK Core Data Standards and unless otherwise specified will include on-treatment and post-treatment data.

A scatter plot of maximum post-baseline ALT vs maximum post-baseline total bilirubin will be produced. In addition, if any liver stopping or liver monitoring events occur during the study, summaries of liver monitoring/stopping event reporting and hepatobiliary laboratory abnormalities will be produced.

Samples for anti-MPO antibody, anti-PR3 antibody, ANA, and antidsDNA antibody are collected at baseline visit and if clinically indicated post baseline, analysed on as needed basis and will be summarised only for participants with data available.

The details of the planned displays will be in OPS.

4.6.3.2. Vital Signs

Pre-dose systolic blood pressure, diastolic blood pressure, pulse rate and body temperature including change from baseline at all visits will be summarised and listed.

4.6.3.3. ECG

Actual and change from baseline (for post-baseline timepoints) values for QTc(F), and heart rate will be summarised by treatment for Screening, Baseline, Week 26, Week 52, and withdrawal visit. ECG results will also be listed. Abnormal findings and interpretations will be listed separately.

Individual maximum QTc(F) values will also be summarised to show the number of subjects with maximum values (msec) in the following categories: <= 450, 450 < to <= 480, 480 < to <= 500 and > 500.

Additionally, individual maximum changes from baseline in QTc(F) values will be summarised to show the number of subjects with maximum changes (msec) in the categories: < -60, ≥ -60 to < -30, ≥ -30 to < 0, ≥ 0 to < 30, ≥ 30 to < 60 and ≥ 60.

All ECG values for participants with protocol defined QT stopping criteria will be listed.

4.6.3.4. Complement

Complement (C3 and C4) will be summarised by parameter and visit and presented as a table and as a figure. The summary table will include baseline concentration, concentrations at each visit and ratio to baseline at each visit. Summary statistics to be presented are n, geometric mean, SD of logs, median, minimum and maximum.

4.7. Immunogenicity Analysis

For the immunogenicity assessment, two types of anti-drug antibody (ADA) assays will be performed, a binding antibody assay and a neutralizing antibody assay (NAb).

For the binding assay, there will be a three-tiered analysis: screening, confirmation and titration. The screening assay produces a result of positive or negative relative to a screening cut point. Positive samples continue with the confirmation assay, which also produces a result of positive or negative relative to a confirmation cut point. For positive confirmation samples, a titre value will also be obtained to quantify the degree of binding in a titration assay, and the sample will be tested with the neutralizing assay, which also reports results as positive or negative. A sample that is positive in the confirmation assay is considered positive for anti-GSK3511294 antibodies.

All participants' baseline immunogenicity samples will be analysed. Post-baseline immunogenicity samples will only be analysed for participants receiving GSK3511294 100 mg SC.

The following descriptive summaries will be presented for GSK3511294 100 mg SC group by visit using mITT population.:

- Summary of binding antibody assay results: it will summarise the binding antibody confirmatory assay results at each visit. Summary will include categories for negative and positive results, sub categories for transient positive and persistent positive (see note below), and available titre values (min, median and max). It will also summarise the highest post-baseline binding antibody confirmatory assay result obtained.
- Summary of binding antibody results for participants without positive result prior to dosing: it will summarise the binding antibody confirmatory assay results at each visit. Summary will include categories for negative and positive results, sub categories for transient positive and persistent positive (see note below), and available titre values (min, median and max). It will also summarise the highest post-baseline binding antibody confirmatory assay result obtained.
- Summary of neutralizing antibody assay results: it will summarise the neutralising antibody assay results for participants with a positive binding antibody confirmatory assay results. Neutralising antibody assay results will be categorised as positive or negative. It will also summarise the highest post-baseline neutralizing antibody assay result obtained.
- Summary of AE by highest post-baseline binding antibody confirmatory assay result

The following descriptive summaries will be presented for the placebo group using mITT population:

- Summary of binding antibody assay results for all baseline visit results. Summary will include categories for negative and positive results, and available titre value (min, median and max).
- Summary of neutralizing antibody assay results for all baseline visit results. Summary will include categories for negative and positive results.

Note: Visits will include pre-dose baseline visit and all post-baseline visits where immunogenicity assessments were performed. The binding antibody confirmatory assay

results are categorised as negative or positive. The positive results will have two sub categories: transient positive (defined as a single confirmatory positive immunogenic response that does not occur at the final study assessment) or persistent positive (defined as a confirmatory positive immunogenic response for at least 2 consecutive assessments or a single result at the final study assessment). For the summary of highest post-baseline binding antibody confirmatory assay result and neutralizing antibody assay result, subjects with both positive and negative results will be identified in the positive category. If a subject had titre results that fall into multiple titre result categories, they will be included in the highest category.

Immunogenicity data will be listed for participants with at least one positive screening binding antibody assay result.

4.8. Healthcare Resource Utilization

The total number of visits per participant for each type of healthcare contact: non inpatient (home visits [day], home visits [night], physician office/clinic visits, urgent care/outpatient clinic visits, emergency room visits, telephone calls, telemedicine consultations) and inpatient admissions (intensive care unit and general hospital wards) will be presented by summarising the respective visits and number of days (Length of Stay-LOS). This will also be summarised for each contact type (asthma-exacerbations, other healthcare contact).

4.9. Interim Analyses

No interim analyses of efficacy data are planned.

An independent data monitoring committee (IDMC) will periodically review unblinded safety data from the three Phase III studies in the program: 206713, 213744 (this study) and 206785, in accordance with the IDMC Charter.

The IDMC will review all safety data, including AEs and serious adverse events (SAEs) and adverse events of special interest (AESI), laboratory parameters, including haematological and clinical chemistry parameters and ECG assessments from the three studies for identification of any potential safety signals. The safety data analyses for the IDMC reviews will be performed by an independent statistician. There are no circumstances under which IDMC review of the data would lead to a recommendation to stop for efficacy. Other than the emergency unblinding procedures described in the protocol, all personnel having direct responsibility for the conduct of the study will remain blinded to treatment groups for all data until the database is frozen.

4.10. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol (Dated: 01-OCT-2020) are detailed in Table 4.

Table 4 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
Safety population is defined for safety analysis	No safety population is defined	Safety population defined in the protocol is the same as the mITT population. mITT population will be used for safety analysis
Protocol Section 9.3 states actual intervention received will be used in the analysis	Randomised intervention will be used in the analysis	Participants will receive randomised intervention at week 26 and 52 only. It is feasible to use randomised intervention in analysis.

5. SAMPLE SIZE DETERMINATION

Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125).

5.1. Sample Size Assumptions

A sample size of 375 participants (2:1 GSK3511294 to placebo allocation ratio) is based on sufficient power to conclude superiority on primary and key secondary endpoints.

5.1.1. Primary Endpoint

The assumed true annualised rate of exacerbations in the placebo arm is 1.18. Based on an assumed true treatment difference of a 50% reduction in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC, a sample size of 375 randomised participants (250 to GSK3511294, 125 to placebo) will provide 99% power for the primary endpoint at a 5% two-sided significance level [PASS, 2020].

The assumptions for the placebo rate and treatment effect are median values from an elicitation exercise which used Phase 3 anti-IL-5/5R historical data (~50% reduction in exacerbations) and expert opinion. The sample size is based also on an assumption of 0.8 for the dispersion parameter which was observed in two mepolizumab studies [Pavord, 2012; Ortega, 2014]. It was assumed that 14% of participant-years data will be missing due to study withdrawal, which is also consistent with mepolizumab studies.

Based on the assumptions above, the minimum observed treatment difference estimated to result in significance at the 5% two-sided significance level is a 27% reduction in exacerbations for GSK3511294 + SoC compared with placebo + SoC (rate ratio of 0.73).

5.1.2. Secondary Endpoints

Table 5 describes the assumptions and power values for two key secondary endpoints. The assumptions are obtained from the Phase 3 mepolizumab studies [Pavord, 2012; Ortega, 2014; Chupp, 2017].

Table 5 Power Calculations for Key Secondary Endpoints

Endpoint	Assumed treatment difference (GSK3511294 + SoC vs. placebo + SoC)	Standard deviation	Power
Change from baseline in SGRQ total score at Week 52	-7	17	96%
Change from baseline in ACQ-5 score at Week 52	-0.35	1.1	83%

5.2. Sample Size Sensitivity

The sample size and power calculations are based on assumptions about the true values for parameters. The power of the study is dependent on changes in these assumptions, in particular the assumed annualised exacerbation rates. Table 6 illustrates how changes in assumptions for two parameters (placebo + SoC annualised exacerbation rate and treatment effect) affect the power.

Table 6 Estimates of Power for Assumed Placebo + SoC Exacerbation Rate and Assumed Percent Reduction with GSK3511294 + SoC Compared with Placebo + SoC

Percent reduction in annualised exacerbation rate with GSK3511294 + SoC vs. placebo + SoC	Placebo + SoC annualised exacerbation rate			
	1.0	1.1	**1.18**	1.3
30%	61	63	65	67
40%	88	90	91	92
50%	98	99	**99**	99

5.3. Sample Size Re-estimation or Adjustment

There will be no sample size re-estimation.

There is a possibility for randomising greater than 375 participants in the study. This is due to local country requests or requirements, for example, the local health authority specifying a minimum number to be enrolled. The primary analysis and clinical study report (CSR) will be based on the initial target enrolment. If the study target enrolment is reached before a local country enrolment requirement is met, then recruitment in that country may continue. Participants from those countries, who have already been enrolled at the time of reaching the target enrolment, will be included in the primary analysis. All data (pre- and post-target enrolment) will be analysed together but reported later in a supplement to the study report. Inferences will be drawn on the original study report based on the target enrolment.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Abbreviations and Trademarks

6.1.1. List of Abbreviations

Abbreviation	Description
ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
ADSD	Asthma Daily Symptom Diary
ANSD	Asthma Nightly Symptom Diary
AE	Adverse Event
AESI	Adverse Event of Special Interest
Anti-IL-5	Anti-Interleukin-5
BP	Blood pressure
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPMS	Clinical Pharmacology Modeling and Simulation
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case report form
ED	Emergency Department
eDiary	Electronic diary
FEV1	Forced expiratory volume in 1 second
GSK	GlaxoSmithKline
HRQoL	health-related quality of life
ICS	Inhaled corticosteroids
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IL-5	Interleukin-5
LOS	Length of Stay
IM	Intramuscular
IV	Intravenous
KR method	Kenward and Roger method
LS Mean	Adjusted mean for the treatment group
LS Mean Change	Adjusted mean change from baseline for the treatment group
MAR	Missing at Random
MNAR	Missing Not at Random
Max	Maximum
MedDRA	Medicinal dictionary for regulatory activities
Min	Minimum
mITT	Modified Intent to Treat
Mg	Milligram
MMRM	Mixed Models Repeated Measures
NAb	Neutralising antibody

NHANES	National Health and Nutrition Examination Survey
OCS	Oral corticosteroids
OPS	Output and Programming Specification
OR	Odds ratio
PD	Pharmacodynamics
PEF	Peak expiratory flow
PT	Preferred Term
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PRO	Patient-reported outcomes
PROMIS	Patient-reported outcomes measurement information system
QTcF	QTc corrected by Fridericia's formula
RAP	Reporting and Analysis Plan
SAP	Statistical Analysis Plan
SAE	Serious adverse event
SAC	Statistical Analysis Complete
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SGRQ	St George's Respiratory Questionnaire
SNOT-22	Sino-nasal Outcomes Test-22
SoC	Standard of care
SOC	System Organ Class

6.1.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies	Trademarks not owned by the GlaxoSmithKline Group of Companies
None	SAS

7. REFERENCES

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TITLE PAGE

Protocol Title: A 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of the efficacy and safety of GSK3511294 (Depemokimab) adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype

Protocol Number:213744

Compound Number: GSK3511294

Short Title: Placebo-controlled efficacy and safety study of GSK3511294 (Depemokimab) in participants with severe asthma with an eosinophilic phenotype

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VERSION HISTORY

Table 1 SAP Version History Summary

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1	22-Jan-2021	Version 01 Approval Date: 01-OCT-2020	Not Applicable	Original version
Amendment 01	02-Aug-2022	Amendment 02 Approval Date: 05-APR 2022	1. Section 1.1.2 Estimand: updated intercurrent event strategy for change in maintenance therapy 2. Section 3 Analysis Sets: Updated text related to enrolled, randomised, full analysis set, and safety population. Added Japan sub-population. 3. Section 4.3.2: updated model checking method 4. Section 4.4.9: removed statistical analysis of PGI-P/PGI-C endpoints 5. Section 4.4.10 ADSD/ANSD: added study 217640 6. Section 4.5.2: updated imputation method for non-detectable blood eosinophil values of 0 GI/L, or results below the limit of quantification. 7. Section 4.6.3.3: adding two visits for ECG reporting and modified wording for categories to be reported 8. Section 4.9: Added unblinded interim analysis for futility and blinded analysis for validation of questionaries 9. Section 4.10:	1. Different strategies to be applied to intercurrent event of change in maintence therapy and use of prohibited medication for PD endpoint. Also added clarification for this intercurrent event. 2. Revision of Analysis sets based on the new SAP template description. To included Japan reporting into this analysis plan. 3. Correct the checking method 4. Only need summary 5. Clarification 6. Clarification 7. Update due to protocol amendment 8. Update due to protocol amendment 9. Update due to protocol amendment 10. Update in order to include all type of corticosteroids use

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			removed that table of 'Changes to Protocol Defined Analyses'. 10. Section 4.4.15: added a summary of systemic corticosteroids use associated with clinically significant exacerbations	
Amendment 02	14-dec-2023	Amendment 02 Approval Date: 05-APR 2022	1. Section 1.1.1 Endpoints and Section 2.1 Multiplicity Adjustment 2. Section 1.1.2 Estimands: updated for the endpoints with descriptive summaries, changed from 'while on treatment strategy' to 'hypothetical strategy. And removed safety endpoints from the table. 3. Section 3 Analysis Sets: updated FAS and Safe analysis sets . Added FAS-modified and Safety-modifitied analysis sets. 4. Section 4.1.2 Baseline Definition: changed from 'Day -7 to Day 1' to 'Day -6 to Day 1' 5. Section 4.2.2, 4.3.2, 4.4, Main Analytical Approach, removed the covariate of ' baseline maintenance OCS therapy (OCS vs. no OCS)' from the analysis model	1. Based on FDA's feedback that for ADSD/ANSD measures to be considered for inclusion in the label they should be elevated in the hierarchy (as secondary endpoints). 2. Clarification. 3. To exclude patients from the sites that had GCP non-compliance/ significant data integrity concern for the main analyses. 4. Clarification 5. This coveraite is not needed because >95% subjects were not on maintenance OCS therapy at baseline. 6. Tipping point analysis will be performed regardless proportion of missing data 7. as planned since MCID for ADSD/ANSD becomes available 8. a figure is needed

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			6. Section 4.2.3.2 removed condition for performing tipping point sensitivity analysis 7. Section 4.4.10.2. Added analysis for responder based ADSD/ANSD 8. Section 4.4.13. Added a PEF plot 9. Section 4.4.15. Removed the sentences regarding summary of number of days with systemic corticosteroids (including OCS, IV and IM) use 10. Section 4.9 Risk Benefit Analysis: added the section to describe planned Risk Benefit forest plot 11. Section 4.3.2, 4.4.3, 4.4.10 added suggestion for how to exclude timepoints from analysis when the model does not converge. 12. Section 4.1.1 added clarification for covaiates 13. Section 4.3.3 added condition for performing analysis	for CSR. 9. Conconmitant medication data shows there is very limited number of IV or IM systemic corticosteroids usage 10. additional plot required for CSR 11. Clarification 12. Clarification 13. Clarification

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
Amendment 03	03 Apr 2024	Amendment 02 Approval Date: 05-APR 2022	1. Section 3, modified Screened population 2. Section 4.1.4 and Section 4.2 & 4.3 Added subgroup definitions and subgroup analyses 3. Section 4.2.3.2 added a condition for performing Tipping Point analysis 4. Section 4.5.2 added summary of AE by subgroups	1. clarification 2. identified new subgroups of interest 3. clarification 4. per EMA feedback to add subgroup summary for safety

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 213744. Details of the planned final analyses are provided.

Descriptive study population analyses such as summary of demography and baseline characteristics and additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Annualised rate of clinically significant exacerbationsa over 52 weeks
Secondary	
• To evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	• Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 52 • Change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at Week 52 • Change from baseline in Asthma Daily Symptom Diary (ADSD)/ Asthma Nightly Symptom Diary (ANSD) weekly mean score at Week 52 • Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks
Other	
• To investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	• Time to first clinically significant exacerbationa • Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit • Change from baseline in SGRQ total score at discrete timepoints during the 52-week period • Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period • SGRQ total score responder status at Week 52 (responder defined as achieving ≥4-point reduction from baseline) • ACQ-5 score responder status at Week 52 (responder defined as achieving ≥0.5-point reduction from baseline) • Change from baseline in Patient-Reported Outcomes Measurement Information Systems (PROMIS)

Objectives	Endpoints
	Fatigue items score at discrete timepoints during the 52-week period • Change from baseline in Asthma Daily Symptom Diary (ADSD)/ Asthma Nightly Symptom Diary (ANSD) weekly mean score at specified timepoints during the 52-week period • ADSD responder status (responder defined as achieving ≥1.2 point reduction from baseline) over the 52-week period • ANSD responder status (responder defined as achieving ≥1.5 point reduction from baseline) over the 52-week period • Change from baseline in awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean • Change from baseline in morning peak expiratory flow (PEF) 2-week mean • Change from baseline in daily asthma symptom scores 2-week mean • Change from baseline in mean number of occasions of rescue medication use/day 2-week mean • Mean number of days with oral corticosteroids (OCS) usage over 52 weeks • Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period • Change from baseline in Sino-nasal Outcomes Test-22 (SNOT-22) score at discrete timepoints during the 52-week period
• To investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient- and clinician-rated response to therapy • patient global impression of asthma severity and its change from baseline	• Patient-rated response to therapy at discrete timepoints during the 52-week period • Clinician-rated response to therapy at discrete timepoints during the 52-week period • Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period • Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during the 52-week period
• To investigate the PD effects of GSK3511294	• Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the 52-week period
• To investigate the PK of GSK3511294	• GSK3511294 plasma concentration at discrete timepoints during the 52-week period
Safety	
• To evaluate the safety and tolerability of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	• Incidence of AEs/SAEs • Laboratory parameters, including haematological and clinical chemistry parameters • Vital signs including blood pressure (BP), body temperature, and pulse rate • ECG assessments • Incidence of immunogenicity as measured by the presence of ADA/NAb to GSK3511294

Objectives	Endpoints
Health Resource Use	
• To further evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on healthcare utilisation on top of existing asthma therapy	• Healthcare utilisation for asthma including hospitalisation, ED, and physician office/clinic visits

a. Clinically significant exacerbations will be defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit. For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

1.1.2. Estimands

Table 2 Estimands

The following two attributes apply to all estimands:

- Treatment comparison: GSK3511294 + SoC compared with placebo + SoC
- Population: Adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype following the strategy outlined below for dealing with the main intercurrent events that are anticipated.

Objectives	**Estimand**		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
Primary objective: To evaluate the efficacy of GSK3511294 100 mg (SC) every 26 weeks versus placebo in participants with severe uncontrolled asthma with an eosinophilic phenotype on top of existing asthma therapy	Annualised rate of clinically significant exacerbations over 52 weeks	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred • Change in maintenance	Ratio of the rates of exacerbations between GSK3511294 + SoC and placebo + SoC.

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	
Secondary objective: to evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on health-related quality of life (HRQoL) and additional efficacy assessments on top of existing asthma therapy	a. Change from baseline in SGRQ total score at Week 52 b. Change from baseline in ACQ-5 score at Week 52 c. Change from baseline in pre-bronchodilator FEV_1 at Week 52 d. Change from baseline in ADSD/ ANSD weekly mean score at Week 52	• Study intervention discontinuation due to reasons unrelated to the COVID-19 pandemic: to be handled with a treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: to be	a. Difference in mean change from baseline in SGRQ total score at Week 52 between GSK3511294 + SoC and placebo + SoC b. Difference in mean change from baseline in ACQ-5 score at Week 52 between GSK3511294 + SoC and placebo + SoC c. Difference in mean change from baseline in pre-

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	e. Annualised rate of clinically significant exacerbations requiring hospitalisation and/or ED visit over 52 weeks	handled with a hypothetical strategy i.e. had the intercurrent event not occurred • Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	bronchodilator FEV_1 at Week 52 between GSK3511294 + SoC and placebo + SoC d. Difference in mean change from baseline in ADSD/ ANSD weekly mean score at Week 52 between GSK3511294 + SoC and placebo + SoC e. Ratio of the rates of clinically significant exacerbations requiring hospitalisation and/or ED visit between GSK3511294 + SoC and placebo + SoC
Other objective: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of	a. Time to first clinically significant exacerbation b. Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event	a. Hazard ratio of first clinically significant exacerbation between GSK3511294 + SoC and placebo + SoC b. Hazard ratio of first

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
existing asthma therapy	c. Change from baseline in SGRQ total score at discrete timepoints during the 52-week period d. Change from baseline in ACQ-5 score at discrete timepoints during the 52-week period e. Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period f. Change from baseline in Sino-nasal Outcomes Test-22 (SNOT-22) score at discrete timepoints during the 52-week period g. Change from baseline in ADSD/ANSD weekly mean score at specified timepoints during the 52-week period	occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred • Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	clinically significant exacerbation requiring hospitalisation and/or ED visit between GSK3511294 + SoC and placebo + SoC c. Difference in mean change from baseline in SGRQ total score at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC d. Difference in mean change from baseline in ACQ-5 score at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC e. Difference in mean change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at discrete timepoints during the 52-week period between GSK3511294 +

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
			SoC and placebo + SoC f. Difference in mean change from baseline SNOT-22 score at discrete timepoints during the 52-week period between GSK3511294 + SoC and placebo + SoC g. Difference in mean change from baseline in ADSD/ ANSD weekly mean score between GSK3511294 + SoC and placebo + SoC
Other objective: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	a. SGRQ total score responder status at Week 52 (responder defined as achieving ≥4-point reduction from baseline) b. ACQ-5 score responder status at Week 52 (responder defined as achieving ≥0.5-point reduction from baseline) c. ADSD responder status (responder defined as	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring • Study intervention discontinuation due to reasons related to the COVID-19 pandemic:	a. Odds ratio in SGRQ total score responder status at Week 52 between GSK3511294 + SoC and placebo + SoC b. Odds ratio in ACQ-5 score responder status at Week 52 between GSK3511294 + SoC and placebo + SoC c. Odds ratio in ADSD responder status over 52 weeks between

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	achieving ≥1.2 point reduction from baseline) over the 52-week period d. ANSD responder status (responder defined as achieving ≥1.5 point reduction from baseline) over the 52-week period	hypothetical strategy i.e. had the intercurrent event not occurred. Status following IE will be set as missing. • Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	GSK3511294 + SoC and placebo + SoC d. Odds ratio in ANSD responder status over 52 weeks between GSK3511294 + SoC and placebo + SoC
• **Other objective**: to investigate GSK3511294 100 mg (SC) every 26 weeks versus placebo on incidence of hospitalisation	a. Change from baseline in PROMIS Fatigue items score at discrete timepoints during the 52-week period b. Change from baseline in	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy	a. Descriptive summary of change from baseline in PROMIS Fatigue items score by treatment group and by visit

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
and/or ED visit and measures of asthma control, night sleep and lung function on top of existing asthma therapy	awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean c. Change from baseline in morning peak expiratory flow (PEF) 2-week mean d. Change from baseline in daily asthma symptom scores 2-week mean e. Change from baseline in mean number of occasions of rescue medication use/day 2 week mean f. Mean number of days with oral corticosteroids (OCS) usage over 52 weeks	i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred. • Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the	b. Descriptive summary of change from baseline in 2-weekly mean awakenings at night due to asthma symptoms requiring rescue medication use by treatment group and by time interval c. Descriptive summary of change from baseline in 2-week mean morning PEF by treatment group and by time interval d. Descriptive summary of change from baseline in daily asthma symptom scores 2-week mean by treatment group and by time interval e. Descriptive summary of change from baseline in 2 week mean number of occasions of rescue medication use/day by treatment group and by

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		intercurrent event occurring •	visit and time interval f. Descriptive summary of mean number of days OCS usage over 52 weeks by treatment group
Other objective: to investigate GSK3511294 versus placebo on top of existing asthma therapy on • patient- and clinician-rated response to therapy	a. Patient-rated response to therapy at discrete timepoints during the 52-week period b. Clinician-rated response to therapy at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred. • Change in maintenance therapy (not important	Descriptive summary of (by treatment group) a. Patient-rated response to therapy at discrete timepoints during the 52-week period b. Clinician-rated response to therapy at discrete timepoints during the 52-week period

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring. Summary will include all on and off treatment data. • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event. occurring. Summary will include all on and off treatment data.	
Other objective: to investigate GSK3511294 versus placebo on top of existing asthma therapy on patient global impression of asthma severity and its change from baseline	a. Patient global impression of severity (PGI-S) of asthma at discrete timepoints during the 52-week period b. Patient global impression of change (PGI-C) from baseline of asthma severity at discrete timepoints during	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: treatment policy strategy i.e. regardless of the intercurrent event occurring	Descriptive summary of (by treatment group) a. PGI-S of asthma at discrete timepoints during the 52-week period b. PGI-C from baseline of asthma severity at discrete

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	the 52-week period	• Study intervention discontinuation due to reasons related to the COVID-19 pandemic: hypothetical strategy i.e. had the intercurrent event not occurred. • Change in maintenance therapy (not important PDs): treatment policy strategy i.e. regardless of the intercurrent event occurring • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): treatment policy strategy i.e. regardless of the intercurrent event occurring	timepoints during the 52-week period
Other objective: to investigate the PD effects of GSK3511294	Ratio to baseline in absolute blood eosinophil count at discrete timepoints during the	• Study intervention discontinuation due to reasons unrelated to the	Ratio in absolute blood eosinophil count GSK3511294

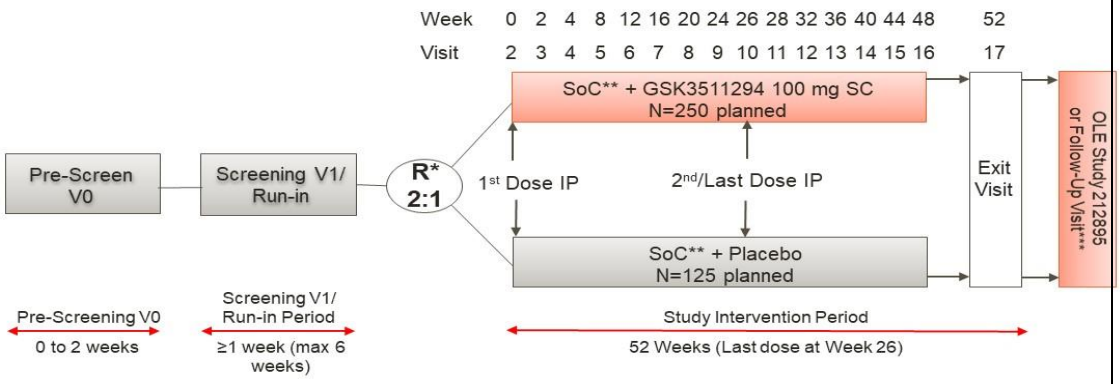
Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
	52-week period	COVID 19 pandemic: while on treatment strategy i.e. only data collected while participant was on-treatment will be used on the analysis. Blood eosinophil counts taken more than 26 weeks following last dose will not be included in the analysis. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: same as above • Change in maintenance therapy(not important PDs): same as above • Concomitant medication important PDs (change in maintenance therapy or use of prohibited medications): hypothetical strategy i.e. had the intercurrent event	+ SoC vs. placebo + SoC

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		not occurred.	
Other objective: to investigate the PK of GSK3511294	GSK3511294 plasma concentration at discrete timepoints during the 52-week period	• Study intervention discontinuation due to reasons unrelated to the COVID 19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Study intervention discontinuation due to reasons related to the COVID-19 pandemic: while on treatment strategy i.e. summarise the variable while the participants actually received their randomised treatment. • Change in maintenance therapy(not important PDs): same as above • Concomitant medication important PDs (change in	Descriptive summarise of GSK3511294 plasma concentration by visit. (GSK3511294 + SoC arm only)

Objectives	Estimand		
	Endpoint	**Intercurrent Event Strategy**	**Population Level Summary Measure**
		maintenance therapy or use of prohibited medications): hypothetical strategy i.e. had the intercurrent event not occurred.	
Health Resource Use: To further evaluate GSK3511294 100 mg (SC) every 26 weeks versus placebo on healthcare utilisation on top of existing asthma therapy	Healthcare utilisation for asthma including hospitalisation (including ICU admissions and Length of Stay-LOS), ED, and physician office/clinic visits (scheduled and unscheduled)	Same strategy as per primary endpoint	Descriptive summary of healthcare utilisation

1.2. Study Design

Overview of Study Design and Key Features



** R = Randomisation: To be randomised participants without a historical blood eosinophil count of ≥300 cells/µL must have a blood eosinophil count of ≥150 cells/µL at Screening Visit 1. Participants will remain on their standard of care (SoC) asthma therapy throughout the intervention period and will be randomised 2:1 to receive GSK3511294 (100 mg) or placebo.*
*** SoC = medium to high dose ICS (≥440 µg FP HFA daily or clinical comparability) plus additional controller. SoC asthma therapy to exclude biologics.*
**** OLE = Open label extension. Willing participants will continue directly into OLE Study 212895. Participants unwilling to continue will have a follow-up visit 4 weeks after the Exit Visit.*

Design Features	• Phase 3A • 52-week treatment period • Randomised • Double-blind • Placebo-controlled • Parallel group • Multi-centre • Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125). • A sample size of 375 randomised will provide 99% power to demonstrate superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC in annualised rate of clinically significant exacerbations over 52 weeks, based on the true annualised rate of exacerbations in the placebo arm being 1.18 , an assumed true treatment difference of a 50% reduction and at a 5% two-sided significance level. • Participants who receive both doses of study intervention and complete the Exit Visit will be eligible to participate in an open-label extension (OLE) study (Study 212895), during which they will receive two doses of open-label GSK3511294 100 mg SC over another 52 weeks.
Study intervention and Study intervention Assignment	The study will consist of a pre-screen period (0-2 weeks), a run-in period (1-6 weeks), and a study intervention period (52 weeks). After the run-in period, participants will be randomised in a 2:1 ratio using an interactive response technology (IRT) system in a blinded manner to receive either GSK3511294 100 mg or placebo by SC injection. Randomisation will be stratified based on baseline ICS dose (medium or high dose). Two doses of study intervention will be administered in the clinic: the first at randomisation Visit 2 (Week 0) and the second at Visit 10 (Week 26). Participants will be assessed at each scheduled visit (a total of 17 study visits) during the 52-week treatment phase. Study visits may be conducted remotely (by a home healthcare professional) or virtually, however, in-person clinic visits are required for the following: pre-screening Visit 0, screening Visit 1, randomisation Visit 2, Visit 3, Visit 10, Visit 11, Exit Visit 17, and WS Visit (if applicable). Participants will remain on their existing stable maintenance asthma therapy throughout the study.
Interim Analysis	• An unblinded interim analysis for futility is planned • Regular IDMC review of safety data are planned.

2. STATISTICAL HYPOTHESES

The primary study objective is to test for the superiority of GSK3511294 100 mg SC + SoC following two doses (at Week 0 and at Week 26) compared with placebo + SoC, assessed by the annualised rate of clinically significant exacerbations measured over the study intervention period of 52 weeks.

The study will test at a 5% two-sided significance level the null hypothesis that there is no difference in annualised exacerbation rate between GSK3511294 and placebo.

2.1. Multiplicity Adjustment

The treatment comparison of interest for the primary and secondary endpoints is GSK3511294 100 mg SC + SoC vs placebo + SoC. A fixed sequence hierarchical testing procedure will be used to provide strong control of Type I error for multiplicity arising from the primary and multiple secondary endpoints. This will be carried out using a stepdown closed testing procedure where inference for an endpoint in the predefined hierarchy will be dependent on statistical significance having been achieved for the previous endpoints in the hierarchy. For example, for the primary endpoint, GSK3511294 + SoC will be compared to placebo + SoC at a two-sided 5% level. The next endpoint in the hierarchy (i.e. the first secondary endpoint) will be tested only if the test for the primary endpoint is significant at the two-sided 5% level. Testing will continue down the hierarchy for the remaining endpoints in an equivalent manner only if the previous endpoint in the hierarchy achieves statistical significance.

The hierarchy of the primary and secondary endpoints to be tested is as follows:

1. Annualised rate of clinically significant exacerbations over 52 weeks
2. Change from baseline in SGRQ at Week 52
3. Change from baseline in ACQ-5 at Week 52
4. Change from baseline in clinic pre-bronchodilator FEV_1 at Week 52
5. Change from baseline in ANSD at Week 52
6. Change from baseline in ADSD at Week 52
7. Annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who sign the ICF (not including subjects who failed at pre-screening).	• Study Population
Enrolled	All participants who entered the study. Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	• Study Population
Randomised	All participants who were randomly assigned to study	• Study Population

Analysis Set	Definition / Criteria	Analyses Evaluated
	intervention in the study.	
Full Analysis Set (FAS)	All randomised participants who receive at least one dose of study intervention excluding participants from sites 250085 & 250523. Data will be analysed according to randomised treatment arm.	• Study Population • Efficacy • Immunogenicity • PD • Health Resource Use
FAS-PROMIS	All participants in the FAS population for whom at least one PROMIS fatigue items were administered	• Efficacy (PROMIS)
FAS-ADSD/ANSD	All participants in the FAS population for whom at least one ADSD/ANSD questionnaire were administered	• Efficacy (ADSD/ANSD)
FAS-Japan	All participants in the FAS population who are enrolled from Japan and with Japanese heritage only	• Study Population • Efficacy • PD
FAS-Non-Japan	All participants in the FAS population who are not in FAS-Japan analysis set	• PD
Safety	All randomised participants who receive at least one dose of study intervention excluding participants from sites 250085 & 250523. Participants will be analysed according to the intervention they are allocated at randomisation, unless a participant receives a different intervention to the randomised intervention at all protocol-defined administrations at which study medication was received, in which case the participant will be analysed according to the actual intervention they received. This population will serve as the primary population for analyses of safety endpoints.	• Safety
Safety-Japan	All participants in the Safety population who are enrolled from Japan and with Japanese heritage only	• Safety
Safety-Non-Japan	All participants in the Safety population who are not in Safety-Japan analysis set	• Not planned in this SAP but flagged for future analysis
PK	All participants in the FAS population for whom at least one pharmacokinetic sample was obtained, analysed and was measurable.	• PK
PK-Japan	All participants in the PK population who are enrolled from Japan and with Japanese heritage only	• PK
PK-Non-Japan	All participants in the PK population who are not in PK- Japan analysis set	• PK
FAS-Modified	All participants in the FAS population plus randomised particiants from sites 250085 & 250523 who receive at least one dose of study intervention.	• Efficacy (Primary and Secondary)
Safety-Modified	All participants in the Safety population plus randomised particiants from sites 250085 & 250523 who received at least one dose of study intervention. Participants will be analysed according to the intervention they are allocated at randomisation, unless a participant receives a different intervention to the randomised intervention at all protocol-defined administrations at which study medication was received, in which case the participant will be analysed according to the actual intervention they received.	• Key Safety
FAS-ADSD/ANSD-Modified	All participants in the FAS-ADSD/ANSD population plus randomised participants from sites 250085 & 250523 who receive at least one dose of study intervention.	• Efficacy (ADSD/ANSD)

Note: GCP non-compliance/significant data integrity concern at Sites 250085 & 250523 was identified.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The Full Analysis Set (FAS) will be used for all Study Population, Efficacy, Immunogenicity and PD analyses, unless otherwise stated. The Safety analysis set will be used for safety analyses, unless otherwise stated. PK analysis sets will be used for PK data analysis. FAS-Japan, Safety-Japan and PK-Japan will be used for Japan outputs. The Output and Programming Specification (OPS) document will provide more details.

Confidence intervals will use 95% confidence intervals (CI) unless otherwise specified.

Unless otherwise specified, continuous data will be summarised using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarised as the number and percentage of participants in each category.

For endpoints that are formally modelled, summary statistics will be provided. In the statistical analysis where covariates are included in the modelling, the following approach will be applied:

- The covariate of exacerbation history is classified as 2, 3, 4+. In the event that exacerbation history is <2, it will be included in the category of '2'.
- For the covariate of baseline pre-bronchodilator % predicted FEV1, screening pre-bronchodilator % predicted FEV1 will be used if baseline value is missing. If both sreeening and baseline pre-bronchodilator % predicted FEV1 are missing, a missing value will be assigned for this covariate.

Where statistical models are used, if there are important departures from the distributional assumptions, transformations of covariates or alternative models may be explored as supporting analyses.

Randomisation is stratified based on baseline ICS dose (medium or high). All statistical models will include this stratum as a covariate. In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the data collected in the CRF, not the assigned stratum at randomization.

Assessments collected at withdrawal visit will be included in summary tables but won't be included in any statistical analysis.

4.1.2. Baseline Definition

Baseline values for visit based assessments and eDiary assessments are defined in Table 3.

Unless otherwise stated, if baseline is missing, no derivation will be performed and baseline will be set to missing.

Table 3 Baseline Definitions & Derivations

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
Efficacy, Health Outcomes and Other			
SGRQ total and domain scores		X	Day 1 pre-dose
ACQ-5		X	Day 1 pre-dose
Pre-bronchodilator FEV_1	X	X	Day 1 pre-dose
Post-bronchodilator FEV_1	X	X	Day 1 pre-dose
PROMIS Fatigue items score		X	Day 1 pre-dose
ADSD/ANSD weekly mean score	X (daily following Screening)		Average of measurements from Day -7 to Day -1 inclusive (at least 4 days must be non-missing)
Awakenings at night due to asthma symptoms requiring rescue medication use 2-week mean	X (daily following Screening)		Average of measurements from Day -7 to Day -1 inclusive (at least 4 days must be non-missing)
Morning PEF 2-week mean	X (daily following Screening)		Average of measurements from Day -6 to Day 1(pre-dose) inclusive (at least 4 days must be non-missing)
Daily asthma symptom scores 2-week mean	X (daily following Screening)		Average of measurements from Day -6 to Day 1(pre-dose) inclusive (at least 4 days must be non-missing)
Mean number of occasions of rescue medication use/day 2-week mean	X (daily following Screening)		Average of measurements from Day -6 to Day 1(pre-dose) inclusive (at least 4 days must be non-missing)
SNOT-22 score		X	Day 1 pre-dose
PGI-S	X	X	Day 1 pre-dose
Safety			
Blood pressure	X	X	Values from most recent assessment prior to first dose of study treatment which records both systolic and diastolic BP
Pulse rate	X	X	Most recent individual value prior to first dose of study treatment
Clinical Chemistry	X	X	Most recent individual value prior to first dose of study treatment
ECG endpoints	X	X	Values from most recent ECG conducted prior to first dose of study treatment
Hematology with differential (including eosinophil count)	X	X	Most recent individual value prior to first dose of study treatment
Other			
Complement C3 and C4		X	Day 1 pre-dose
Immunogenicity		X	Day 1 pre-dose

NOTES :

- Only records that have been assigned a treatment phase of 'pre-treatment' will be considered as baseline assessments.
- ADSD is to be completed before going to bed and refers to asthma symptoms during the day. Day 1 assessment of ADSD will not be pre-dose. Therefore an average of measurements from Day -7 to Day -1 is defined as the baseline for ADSD/ANSD.
- Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

4.1.3. Multicenter Studies

For the purposes of covariate adjustment in the statistical analysis, countries will be grouped into regions. The following regions are defined:

- European (Czechia, France, Hungary, Italy, Poland, Spain)
- US
- Rest of World (Australia, Canada, Puerto Rico, Japan, Taiwan)

If there are insufficient subjects in each region for the statistical procedures to converge satisfactorily, the combining of regions will be considered.

4.1.4. Subgroups of Interest

Table 4 specifies the subgroups of interest to be used in summary or analyses and the subgroup categories.

Table 4 Subgroups of Interest

Subgroup	Category
Age 1	12-17, 18-64, >=65
Age 2	12-17, >=18
Age 3	12-17, 18-64, 65-74, >=75
Gender	Male, Female
Weight	4 categories determined by quartiles of weight at baseline from the study data
Race	American Indian or Alaska Native, Asian , Black or African American, Native Hawaian or Other Pacific Islander, White, Mixed
Region	European (Czechia, France, Hungary, Italy, Poland, Spain), US, Rest of the World (Australia, Canada, Puerto Rico, Japan, Taiwan)
Baseline ICS Dose	Medium, High
Baseline Eosinophil Supgroup 1	<0.15, >=0.15 cells/uL
Baseline Eosinophil Subgroup 2	<0.30, >=0.30 cells/uL
Baseline ACQ-5	<1.5, >=1.5

Sample size may be small for some subgroup analyses. All sub-group statistical analysis results should be interpreted with caution, especially those with small sample size. If the number of participants is too small (ie. <20) within a category of a subgroup, then the categories may be refined or only summary statistics will be produced.

4.2. Primary Endpoint Analyses

4.2.1. Definition of endpoint

The primary endpoint is the annualized rate of clinically significant exacerbations over the 52 weeks following randomisation.

Clinically significant exacerbations of asthma are defined as worsening of asthma requiring the use of systemic corticosteroids (IM, IV or oral) and/or hospitalisation and/or ED visit (see protocol Section 8.2.2). For all participants, IV or oral steroids (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For participants on maintenance systemic CSs, at least double the existing maintenance dose for at least 3 days is required.

Exacerbations recorded in the eCRF are considered as verified clinically significant exacerbations and will be included in the primary analysis.

Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

4.2.2. Main analytical approach

Primary Statistical Analyses
Endpoint(s)
• Annualized rate of clinically significant exacerbations over 52 weeks
Model Specification

• Generalized linear model assuming a negative binomial distribution
• Terms in the model:
  • Response: number of recorded clinically significant exacerbations experienced per subject.
  • Categorical: treatment group, exacerbation history (variable (2, 3, 4+)), baseline ICS dose (medium, high), geographical region
  • Continuous: baseline pre-bronchodilator % predicted FEV_1
  • Offset: Log_e(total time in the study in years)

Model Checking & Diagnostics
• The fit of the regression models will be examined using “Q-Q” plots of the standardized residuals. Interpretation of these plots will be aided by the addition of simulation-generated tolerance boundaries.
Results Presentation
• Treatment group model estimated annualized exacerbation rates and associated 95% CI • pairwise treatment rate ratios and associated p-value and 95% CI. • pairwise treatment percent reductions in annual exacerbation rate and associated 95% CI
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed “missing at random” (MAR) (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the primary endpoint, the data for the period following withdrawal will be assumed MAR (based on all data included in the analysis under the current estimand strategy).
Subgroup Analysis
• By baseline ICS dose (medium, high), by baseline eosinophil subgroup 1 (<0.15, >=0.15), by baseline eosinophil subgroup 2 (<0.30, >=0.30) and by baseline ACQ-5 (<1.5, >=1.5) subgroup analyses will be performed for FAS analysis set. • For subgroup analysis, subgroup, subgroup*treatment group and subgroup*visit*treatment group terms will be included in each of subgroup analysis model.

Primary Statistical Analyses
• In the event the subgroup analysis model fails to converge, model simplification methods may be addressed (i.e. adjusting covariate structure, streamlining timepoints, combining subgroups, running model separately for subgroup). • A forest plot will be produced to present estimated treatment differences and 95% CIs at week 52 • including all subgroups (including P-value for subgroup*treatment group interaction) • Annualized rate of clinically significant exacerbations over each of 13 week interval will also be performed.
Additional Analysis
The same primary endpoint analysis will be performed using FAS-modified analysis set

4.2.3. Sensitivity analyses

For the main analytical approach, data that is missing due to study withdrawal is assumed to be missing at random. The aim of sensitivity analyses is to assess the robustness in the treatment effect and conclusion in the main analytical approach when departing from the missing at random assumption. Two sensitivity analyses will be performed for this investigation.

4.2.3.1. Sensitivity Analysis 1 (MNAR Based on off-treatment Data)

This sensitivity analysis will be performed where subjects who withdrew from the study early will have missing data imputed for the period of time between withdrawal from the study to the Week 52 visit based on the off-treatment data collected from subjects who continued in the study following discontinuation of randomised intervention. Multiple imputation methods will be used with results combined across imputations using Rubin's method [Roger, 2018].

If the total unobserved/excluded time in the study is <3% of the total study duration or if <50% of the total off-treatment period is observed then the sensitivity analysis will not be conducted.

4.2.3.2. Sensitivity Analysis 2 (Tipping Point Analysis)

Tipping point analysis will explore the impact of missing data by using differing assumptions regarding the exacerbation rate in subjects who withdraw from the study. Subjects who withdrew from study early will have missing data imputed for the period of time between withdrawal from the study to the Week 52 visit based on a range of values for the rate of exacerbations per year following study withdrawal. The values to be investigated will be based on increases relative to the estimated rates obtained within each arm under the MAR assumption. The imputed exacerbation rates will vary independently for the active and placebo arms, and will include scenarios where subjects in the active arm have worse outcomes following early withdrawal from the study than subjects in the placebo arm. The tipping point multiple imputation method will be based on pattern mixture models [Keene, 2014]. The results from the analyses of each sample are combined using Rubin's method.
If the test for the endpoint is not significant at the two-sided 5% level, then the sensitivity analysis for the endpoint will not be performed.

4.3. Secondary Endpoints Analyses

4.3.1. Definition of endpoint(s)

The secondary endpoints are:

- Change from baseline in SGRQ total score at Week 52
- Change from baseline in ACQ-5 score at Week 52
- Change from baseline in pre-bronchodilator FEV_1 at Week 52
- Change from baseline in ANSD at Week 52 (see Section 4.4.10)
- Change from baseline in ADSD at Week 52 (see Section 4.4.10)
- Annualised rate of exacerbations requiring hospitalisation and/or Emergency Department (ED) visit over 52 weeks

4.3.2. Main analytical approach for SGRQ total score, ACQ-5 score and pre-bronchodilator FEV_1

Secondary Endpoints Analyses
Endpoint(s)
• Change from baseline in SGRQ total score at Week 52 • Change from baseline in ACQ-5 score at Week 52 • Change from baseline in pre-bronchodilator FEV_1 at Week 52
Model Specification
• Mixed Models Repeated Measures (MMRM) model. • Terms in the model: **Response**: SGRQ Total score or ACQ-5 score or pre-bronchodilator FEV1 at each visit. **Categorical**: treatment group, exacerbation, baseline ICS dose (medium or high), exacerbation history (variable (2, 3, 4+)), geographical region, visit **Continuous**: baseline (SGRQ Total score, or ACQ-5 score,or baseline pre-bronchodilator FEV1), baseline pre-bronchodilator % predicted FEV1 (for SGRQ total score and ACQ-5 endpoints only) **Interaction**: baseline*visit, treatment group*visit **Repeated**: visit • The MMRM analysis for SGRQ total scores will include data collected at Weeks 4, 12, 26, 40 and 52. • The MMRM analysis for ACQ-5 score will include data collected at Weeks 2, 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48 and 52. In the event the model fails to run due to too many assessment timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest. Suggested order for dropping timepoints is week 44, 20, 36, 16, 32, 8, 48, 24, 28. • The MMRM analysis for pre-bronchodilator FEV1 will include data collected at Weeks 26 and 52. • The model will be fit with an unstructured variance-covariance matrix. • The Kenward and Roger method (KR) for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. In the event the model fails to run using the KR method, then the residual method will be used instead. In the event the model fails to run using residual method and assessments are from many timepoints, timepoints included in the analysis may be reduced by keeping the timepoints/intervals of most interest. • Baseline is defined in Section 4.1.2 • Two models will be fitted; one with a response variable of change from baseline and one with the response variable as the raw value.
Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence

Secondary Endpoints Analyses
that the model assumptions are reasonable.
Results Presentation
• Least-square (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI and P-values for each visit will be presented. • The LS mean treatment differences (and associated 95% CIs) for all visits will also be presented graphically. • SGRQ total scores, ACQ-5 score and pre-bronchodilator FEV1 (absolute value and changes from baseline) will also be summarised by treatment group and visit.
• **Handling of missing data and data excluded due to intercurrent events**
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).
Additional Analysis
The same secondary endpoint analyses will be performed using FAS-modified analysis set
Subgroup Analysis
• by baseline eosinophil subgroup 1 (<0.15, >=0.15), by baseline eosinophil subgroup 2 (<0.30, >=0.30) and by baseline ACQ-5 (<1.5, >=1.5) subgroup analyses will be performed for FAS analysis set . • For subgroup analysis, subgroup, subgroup*treatment group and subgroup*visit*treatment group terms will be included in each of subgroup analysis model. • In the event the subgroup analysis model fails to converge, model simplification methods may be addressed (i.e. adjusting covariate structure, streamlining timepoints, combining subgroups, running model separately for subgroup). • A forest plot will be produced to present estimated treatment differences and 95% CIs at week 52 including all subgroups (including P-value for subgroup*treatment group interaction)

4.3.3. Main analytical approach for annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks

The annualised rate of exacerbations requiring hospitalisation and/or ED visit over 52 weeks will be analysed using a negative binomial generalised linear model, as described for the primary endpoint, Section 4.2.2 for details. This endpoint would only be analysed in the event that a total of 20 or more exacerbations requiring hospitalisation and/or ED visit occurred in the study.

4.3.4. Sensitivity analyses

The sensitivity analyses for the primary endpoint as described in Section 4.2.3 will also be performed for the secondary endpoints.

4.4. Other Endpoints Analyses

4.4.1. Time to first clinically significant exacerbation and Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit

Other Endpoints Analyses
Endpoint(s)
• Time to first clinically significant exacerbation • Time to first clinically significant exacerbation requiring hospitalisation and/or ED visit

Other Endpoints Analyses
Model Specification
• Cox's proportional hazards model • Terms in the model: **Response**: time to first clinically significant exacerbation or first clinically significant exacerbation requiring hospitalization and/or ED visit **Categorical**: treatment group, exacerbation exacerbation history (variable (2, 3, 4+)), baseline ICS dose (medium, high), geographical region **Continuous**: baseline pre-bronchodilator % predicted FEV_1 • The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead. • Kaplan-Meier survivor functions will be obtained for each treatment group using PROC LIFETEST with a TIME statement.
Model Checking & Diagnostics
• The proportional hazards assumption will be examined by obtaining the Kaplan-Meier estimates of the survival function S(t) over time separately for each treatment group. In addition, the ln (-ln[S(t)]) plot will be produced.
Results Presentation
• Hazard ratios and the percent reduction in risk for the pairwise treatment comparisons with associated 95% CIs and p-values will be presented. • The Kaplan-Meier curves will be presented showing the probability of having an event over time for each treatment group separately plotted on the same figure.
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.2. Change from baseline in SGRQ total score and in ACQ-5 score at discrete timepoints during the 52-week period

Analytic approach for change from baseline in SGRQ total score and change from baseline in ACQ-5 score at discrete timepoints during the 52-week period has been included in the secondary endpoints analyse, see Section 4.3.2 for details.

4.4.3. SGRQ total score responder status at Week 52 and ACQ-5 score responder status at Week 52

Other Endpoints Analyses
Endpoint(s)
• Proportion of responders according to SGRQ total score (responder defined as achieving ≥4-point reduction from baseline) • Proportion of responders according to ACQ-5 score (responder defined as achieving ≥0.5-point reduction from baseline)
Model Specification
• Generalized linear mixed model • Terms in the model: **Dependent**: response (yes/no) **Categorical**: treatment group, exacerbation baseline ICS dose (medium or high), exacerbation history (variable (2, 3, 4+)), geographical region, visit, subject **Continuous**: baseline (SGRQ Total score, or ACQ-5 score), baseline pre-bronchodilator % predicted FEV1 **Interaction**: baseline (SGRQ Total score, or ACQ-5 score)*visit, treatment group*visit The model will be fit with an unstructured variance-covariance matrix with one single model to include all visits where the assessment in question is scheduled to be performed.

• Computation of confidence intervals for the odds ratios is based on the individual Wald tests. • The analysis of responder based on SGRQ total scores will include data collected at Weeks 4, 12, 26, 40 and 52. • The analysis of responder based on ACQ-5 score will include data collected at Weeks 2, 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48 and 52. In the event the model fails to run due to too many assessment timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest. Suggested order for dropping timepoints is week 44, 20, 36, 16, 32, 8, 48, 24, 28.
Model Checking & Diagnostics
• Pearson residuals will be plotted by using PLOTS=PEARSONPANEL option for the model statement in SAS.
Results Presentation
• Number and percentage of responders and non-responders for each treatment at each visit • Odds ratio for pairwise comparisons with associated 95 % CIs and p-values
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.4. Change from baseline in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1

Analytic approach for change from baseline in pre-bronchodilator FEV_1 at discrete timepoints during the 52-week period has been included in the secondary endpoint analysis of change from baseline in pre-bronchodilator FEV_1 at Week 52, see Section 4.3.2 for details.

Change from baseline in post-bronchodilator FEV_1 at discrete timepoints during the 52-week period will be analyzed in the same approach as for change from baseline in pre-bronchodilator FEV_1.

4.4.5. PROMIS Fatigue items score

PROMIS Fatigue items score and change from baseline in PROMIS Fatigue items score will be summaried by treatment group and visit.

4.4.6. SNOT-22 score

The SNOT-22 questionnaire is administered (post randomisation) at Week 26 and 52. The 22 questions of the SNOT-22 are each graded on a 6-point scale ranging from 0 = ‘no symptoms’ to 5 = ‘as bad as things could be’. The scores for each of the questions are summed to derive the total score which ranges from 0 to 110, with higher scores representing worse quality of life.

Other Endpoints Analyses
Endpoint(s)
• Change from baseline in SNOT-22 total score at Week 26 and Week 52
Model Specification, Model Checking & Diagnostics
• See Model Specification, Model Checking & Diagnostics for secondary endpoints statistical analyses • analysis will include data collected at Weeks 26 and 52.
Model Results Presentation
• See Model Results Presentation for secondary endpoints statistical analyses (figures will not be presented) • SNOT-22 score (absolute value and changes from baseline) will also be summarised by treatment group and visit.

Other Endpoints Analyses
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.7. Patient-rated response to therapy during the 52-week period

This is an overall evaluation of response to treatment, conducted by the participant at Week 12, 26, 40 and 52 using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse
Patients rated response to therapy will be summarised by treatment group and visit.

4.4.8. Clinician-rated response to therapy during the 52-week period

This is an overall evaluation of response to treatment, conducted by the investigator at Week 12, 26, 40 and 52 using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse
Clinician rated response to therapy will be summarised by treatment group and visit.

4.4.9. Patient Global Impression of Asthma Severity/Change (PGI-S, PGI-C)

Patient Global Impression of Asthma Severity (PGI-S): The participant will complete a PGI-S question at the visits: Randomisation and Screening, Day 1, Week 12, 20, 26, 40, 52. This single global question will ask participants to rate their asthma severity on a five-point scale (no symptoms, mild, moderate, severe, very severe). Responses will be captured electronically.

Patient Global Impression of Change (PGI-C) from Baseline of Asthma Severity: The participant will complete a PGI-C question from baseline of their asthma severity at Week 12, 20, 26, 40 and 52. The single question will ask participants to rate the overall

change in their asthma severity compared with Day 1 (randomisation) prior to start of study intervention. The rating will use a five-point scale (much better, a little better, no change, a little worse, much worse) and responses will be captured electronically.

PGI-S and PGI-C responses will be summarised by treatment group and visit.

4.4.10. ADSD/ANSD

The ADSD/ANSD is a 6-item self-administered patient-reported diary developed by the PRO Consortium's Asthma Working Group (in accordance with the Food and Drug Administration's PRO Guidance) to facilitate comprehensive and reliable assessment of asthma symptoms from a patient's perspective which received qualification from the FDA in March 2019 supporting use in drug development as an exploratory measure.

The ADSD/ANSD is intended for use by adults and adolescents (aged 12 years and older) who are diagnosed with asthma to rate the severity of their symptoms in the three core categories: breathing symptoms (wheezing, shortness of breath), chest symptoms (chest tightness, chest pain) and cough.

The ADSD/ANSD must be completed twice daily by the participant daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.:

- The morning diary (ADSD) is to be completed upon waking and refers to asthma symptoms during the night-time.
- The evening diary (ANSD) is to be completed before going to bed and refers to asthma symptoms during the day.

Participants are required to rate the six symptoms at their worst during the respective timeframes using an 11-point numeric rating scale (NRS) ranging from 0 ('None') to 10 ('As bad as you can imagine'). Responses will be captured electronically.

4.4.10.1. ADSD/ANSD Change from Baseline

Secondary and Other Endpoints Analyses
Endpoint(s)
• Change from baseline in Asthma Daily Symptom Diary (ADSD) weekly mean score at timepoints during the 52-week period (weekly up to Week 16 and then every visit) • Change from baseline in Asthma Nightly Symptom Diary (ANSD) weekly mean score at timepoints during the 52-week period (weekly up to Week 16 and then every visit)
Model Specification, Model Checking & Diagnostics
• Similar to model specification, model checking and diagnostics detailed in Section 4.3.2 • Response variable: weekly mean scores • Baseline score is defined in Section 4.1.2 • In the event the model fails to run due to too many assessment timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest. Suggested order for dropping timepoints is every other week prior to week 16. If the model still does not converge, then drop week 44, 20, 36, 32, 48, 24, 28.
Model Results Presentation
• LS means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI and P-values for each Week will be presented. • The LS mean treatment differences (and associated 95% CIs) for all weeks will also be presented graphically.

• ADSD and ANSD weekly mean absolute score and changes from baseline will also be summarised by treatment group and visit. Summary will include weekly mean score at all visits (including all weeks prior to week 16). .
Handling of missing data and data excluded due to intercurrent events
Same approach as described in Section 4.3.2
Additional Analysis
The same secondary endpoint analyses will be performed using FAS-ADSD/ANSD-modified analysis set

4.4.10.2. Responder Based on ADSD/ANSD

Endpoint(s)
• Proportion of responders according to ADSD weekly mean score (responder defined as achieving ≥1.2 point reduction from baseline) • Proportion of responders according to ANSD weekly mean score (responder defined as achieving ≥1.5 point reduction from baseline)
Model Specification
Generalized linear mixed model • Terms in the model: **Dependent**: response (yes/no) **Categorical**: treatment group, baseline ICS dose (medium or high), exacerbation history (variable (2, 3, 4+)), geographical region, visit, subject **Continuous**: baseline weekly mean score (ADSD/ANSD) **Interaction**: baseline weekly mean score (ADSD/ANSD)*visit, treatment group*visit • The model will be fit with an unstructured variance-covariance matrix with one single model to include all visits where the assessment in question is scheduled to be performed. • Computation of confidence intervals for the odds ratios is based on the individual Wald tests. • The analysis of responder based on SGRQ total scores will include ADSD/ANSD weekly mean score at Weeks 2, 4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40, 44, 48 and 52. • In the event the model fails to run due to too many assessment timepoints, timepoints included in the analysis may be reduced by keeping the timepoints of most interest. Suggested order for dropping timepoints is every other week prior to week 16. If the model still does not converge, then drop week 44, 20, 36, 32, 48, 24, 28.
Model Checking & Diagnostics
• Pearson residuals will be plotted by using PLOTS=PEARSONPANEL option for the model statement in SAS.
Results Presentation
• Number and percentage of responders and non-responders for each treatment at each visit Odds ratio for pairwise comparisons with associated 95 % CIs and p-values
Handling of missing data and data excluded due to intercurrent events
• For participants that discontinue study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event will be excluded from the analysis. Data for this period will be assumed MAR (based on all data included in the analysis under the current estimand strategy). • For participants that withdraw from the study, preventing assessment of the endpoint, the data for the period following withdrawal will be assumed MAR (using data collected under the proposed estimand strategy).

4.4.11. Mean number of occasions of rescue medication per day

Daily diary data for rescue medication (salbutamol/albuterol) use will be aggregated over 2-week periods, then the mean daily usage, excluding days with missing data, will be calculated for each 2-week period (Weeks 1-2, 3-4,…, 51-52). Data for each 2-week period, and change from baseline for each 2-week period will be summarised by treatment group and visit. For definition of baseline see Section 4.1.2.

4.4.12. Awakenings at night due to asthma symptoms requiring rescue medication use

Awakening at night due to asthma symptoms requiring rescue medication use will be summarised as for rescue medication use, see Section 4.4.11.

4.4.13. Morning peak expiratory flow (PEF)

Morning PEF will be summarised as for rescue medication use, see Section 4.4.11.

The summaries will be for :

1. all data included as per FAS population
2. excluding data where asthma medication was taken within 6 hours prior to PEF assessment

The mean change from baseline and associated 95% CIs in morning PEF at all timepoints for the treatment groups will also be presented graphically (for all data).

4.4.14. Daily asthma symptom scores

Daily asthma symptom score will be summarised as for rescue medication use, see Section 4.4.11.

4.4.15. Number of days with oral corticosteroids

Total number of days of oral corticosteroids (OCS) use over 52 weeks that are associated with clinically significant exacerbations per subject will be summarised by treatment group. Also, number of clinically significant exacerbations, number of clinically significant exacerbations treated with OCS, and mean number of days using OCS per clinically significant exacerbations treated with OCS will be summarised by treatment group.

Number of subjects on maintenance OCS at screening, total number of days of maintenance OCS use over 52 weeks and mean number of days of maintenance OCS use per subject will also be summarised by treatment group.

4.5. CLINICAL PHARMACOLOGY DATA ANALYSES

4.5.1. Pharmacokinetic Analyses

In this study, GSK3511294 plasma concentration are collected at discrete timepoints during the 52-week treatment period. GSK3511294 plasma concentration will be summarised by visit. (GSK3511294 + SoC arm only).

The PK data from this study will be included in a meta-analysis of the PK and PKPD data across all GSK3511294 studies. Details of meta-analysis will be in a separate CPMS analysis plan.

4.5.2. Pharmacodynamic Analyses - Blood Eosinophils

Blood eosinophil counts will be loge-transformed prior to analysis. Non-detectable blood eosinophil values of 0 GI/L, or results below the limit of quantification will be imputed with a value of 0.005GI/L prior to log transformation.

Ratio to baseline during W52 will be analysed using a MMRM analysis. Model specification, model checking and diagnostics are the same as described for secondary endpoints statistical analyses, see Section 4.3.1. Analysis will include data from all visits that blood eosinophils data is collected. LS Mean (SE) and LS Mean ratio to screening (SE) in each treatment group will be presented. Mean treatment ratio and 95% CI for GSK3511294 vs placebo will also be presented.

Absolute and ratio to baseline blood eosinophil counts will be summarised by treatment group and visit. Only results from the central laboratory will be included in the summary.

4.6. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set unless otherwise specified. Summaries of data will report data according to the nominal visit for which it was recorded. Occurrence of Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESIs), laboratory data, vital signs, and ECGs will be included in data displays in the form of frequency tables, summary statistics, graphs, and statistical analyses where appropriate.

4.6.1. Extent of Exposure

Two doses of study treatment will be administered during study treatment period: the first at randomisation Visit 2 (Week 0) and the second at Visit 10 (Week 26). Each dose is viewed as providing therapeutic coverage for 26 weeks (182 days). The number of treatments administered and the number of days exposure will be summarised descriptively and listed. Total subject-year exposure will also be presented.

Number of days of exposure to study treatment will be calculated as follow:

Duration of Exposure in Days = (Date of Final Dose) – (Date of First Dose) + 182

Subject years exposure is calculated as follow:

Subject Years Exposure = ((Date of Final Dose) – (Date of First Dose) + 182)/365.25

The exposure summary will also be presented by age subgroup (12-17, 18-64, ≥65).

4.6.2. Adverse Events

Adverse events analyses including the analysis of adverse events (AEs), Serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards.

An overview summary of AEs, including counts and percentages of participants with any AE, AEs related to study intervention, AEs leading to permanent discontinuation of study intervention or withdrawal from study, study intervention related AEs leading to

permanent discontinuation of study intervention or withdrawal from study, SAEs, SAEs related to study intervention, fatal SAEs, and fatal SAEs related to study intervention will be produced. These summaries will also be produced by age subgroup (12-17, 18-64, ≥65).

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

The frequency and percentage of AEs will be summarised in two ways: 1) in descending order by System Organ Class (SOC) and Preferred Term (PT), where exposure-adjusted incidence rate will also be summarised. 2) in descending order by PT only.

Common (>=3%) on treatment AEs will be summarised by overall frequency and summarised by time to onset.

A separate summary will be provided for study intervention-related AEs. A study intervention-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study intervention as 'Yes' or missing. The summary table will be displayed in descending order by SOC and PT.

AE will also be summarised by subgroups of age 1, age 2, age 3, gender, race and region by SOC and PT.

All SAEs will be tabulated based on the number and percentage of participants who experienced the event. Separate summaries will also be provided for study intervention-related SAEs. The summary tables will be displayed in descending order by SOC and PT.

A study intervention-related SAE is defined as an SAE for which the investigator classifies the relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study intervention as 'Yes' or missing. The summary table will be displayed in descending order by SOC and PT.

4.6.2.1. Adverse Events of Special Interest

Adverse events of special interest (AESI) for GSK3511294 program include:

- Allergic (Type 1 hypersensitivity) reactions including anaphylaxis

Note: these events will be assessed by the investigator as to whether they meet the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis.

- Type III hypersensitivity (immune complex disease/vasculitis) reactions
- Local injection site reactions
- QTc prolongation

AESI reported by the investigator as systemic reactions (further categorised by the investigator as either allergic [type I hypersensitivity] or other systemic reactions and assessed against Sampson criteria for anaphylaxis) are collected via targeted eCRF within the study. Vasculitis events and local injection site reactions are also collected via targeted eCRF within the study.

Separate summary tables showing the number and percent of subjects with each type of AESI (excluding QTc prolongation) broken down by preferred term will be created.

For each type of AESI (excluding QTc prolongation) a profile summary table will be produced containing information including, but not limited to, the number of occurrences of the event, event characteristics, time to onset, intensity, outcome and action taken.

A summary of the incidence of serious adverse events and adverse events of special interest (excluding QTc prolongation) will be produced displaying the relative risk and risk difference and their 95% CIs between and GSK3511294 and placebo.

AESI of QTc prolongation will be summarised as detailed in Section 4.6.3.3 ECG.

4.6.3. Additional Safety Assessments

4.6.3.1. Laboratory Data

Summaries of laboratory data including chemistry and haematology parameters, and liver chemistry test data will be based on GSK Core Data Standards and unless otherwise specified will include on-treatment and post-treatment data.

A scatter plot of maximum post-baseline ALT vs maximum post-baseline total bilirubin will be produced. In addition, if any liver stopping or liver monitoring events occur during the study, summaries of liver monitoring/stopping event reporting and hepatobiliary laboratory abnormalities will be produced.

Samples for anti-MPO antibody, anti-PR3 antibody, ANA, and antidsDNA antibody are collected at baseline visit and if clinically indicated post baseline, analysed on as needed basis and will be summarised only for participants with data available.

The details of the planned displays will be in OPS.

4.6.3.2. Vital Signs

Pre-dose systolic blood pressure, diastolic blood pressure, pulse rate and body temperature including change from baseline at all visits will be summarised.

4.6.3.3. ECG

Change from baseline (for post-baseline timepoints) values for QTc(F), and heart rate will be summarised by treatment for Baseline, Week 2,Week 26, Week 28, and Week 52. ECG findings will be summariesd by visit.

Individual maximum QTc(F) values will also be summarised to show the number of subjects with maximum values (msec) post-baseline relative to baseline in the following

categories: Decrease, no change or increase to <= 450, increase to 450 < to <= 480, increase to 480 < to <= 500, increase to 500< to <=530 and increase to > 530. QT uncorrected values will be summarised to show the number of subjects with maximum values (msec) post-baseline relative to baseline in the following categories: Decrease, no change or increase to <600 and increase to >=600.

Additionally, individual maximum changes from baseline in QTc(F) values will be summarised to show the number of subjects with maximum changes (msec) in the categories: increase of <= 30, increase of 31 to 60 and increase of > 60.

All ECG values for participants with protocol defined QT stopping criteria will be listed.

4.6.3.4. Complement

Complement (C3 and C4) will be summarised by parameter and visit and presented as a table. The summary table will include baseline concentration, concentrations at each visit and ratio to baseline at each visit. Summary statistics to be presented are n, geometric mean, SD of logs, median, minimum and maximum.

4.6.4. Additional Safety Analyses

The following additional safety analysis will be provided on Safety-Modified analysis set:

- Overview of all adverse events (including sites 250085 & 250523)
- Summary of on-treatment serious adverse events and adverse events of special interest: incidence, relative risk and risk difference (including sites 250085 & 250523)
- Listing of all adverse events from sites 250085 & 250523

4.7. Immunogenicity Analyses

For the immunogenicity assessment, two types of anti-drug antibody (ADA) assays will be performed, a binding antibody assay and a neutralizing antibody assay (NAb).

For the binding assay, there will be a three-tiered analysis: screening, confirmation and titration. The screening assay produces a result of positive or negative relative to a screening cut point. Positive samples continue with the confirmation assay, which also produces a result of positive or negative relative to a confirmation cut point. For positive confirmation samples, a titre value will also be obtained to quantify the degree of binding in a titration assay, and the sample will be tested with the neutralizing assay, which also reports results as positive or negative. A sample that is positive in the confirmation assay is considered positive for anti-GSK3511294 antibodies.

All participants' baseline immunogenicity samples will be analysed. Post-baseline immunogenicity samples will only be analysed for participants receiving GSK3511294 100 mg SC.

The following descriptive summaries will be presented for GSK3511294 100 mg SC group by visit using FAS population.:

- Summary of binding antibody assay results: it will summarise the binding antibody confirmatory assay results at each visit. Summary will include categories for negative and positive results, sub categories for transient positive and persistent positive (see note below), and available titre values (min, median and max). It will also summarise the highest post-baseline binding antibody confirmatory assay result obtained.
- Summary of binding antibody results for participants without positive result prior to dosing: it will summarise the binding antibody confirmatory assay results at each visit. Summary will include categories for negative and positive results, sub categories for transient positive and persistent positive (see note below), and available titre values (min, median and max). It will also summarise the highest post-baseline binding antibody confirmatory assay result obtained.
- Summary of neutralizing antibody assay results: it will summarise the neutralising antibody assay results for participants with a positive binding antibody confirmatory assay results. Neutralising antibody assay results will be categorised as positive or negative. It will also summarise the highest post-baseline neutralizing antibody assay result obtained.
- Summary of AE by highest post-baseline binding antibody confirmatory assay result

The following descriptive summaries will be presented for the placebo group using FAS population:

- Summary of binding antibody assay results for all baseline visit results. Summary will include categories for negative and positive results, and available titre value (min, median and max).
- Summary of neutralizing antibody assay results for all baseline visit results. Summary will include categories for negative and positive results.

Note: Visits will include pre-dose baseline visit and all post-baseline visits where immunogenicity assessments were performed. The binding antibody confirmatory assay results are categorised as negative or positive. The positive results will have two sub categories: transient positive (defined as a single confirmatory positive immunogenic response that does not occur at the final study assessment) or persistent positive (defined as a confirmatory positive immunogenic response for at least 2 consecutive assessments or a single result at the final study assessment). For the summary of highest post-baseline binding antibody confirmatory assay result and neutralizing antibody assay result, subjects with both positive and negative results will be identified in the positive category. If a subject had titre results that fall into multiple titre result categories, they will be included in the highest category.

4.8. Healthcare Resource Utilization

The total number of visits per participant for each type of healthcare contact: non inpatient (home visits [day], home visits [night], physician office/clinic visits, urgent care/outpatient clinic visits, emergency room visits, telephone calls, telemedicine

consultations) and inpatient admissions (intensive care unit and general hospital wards) will be presented by summarising the respective visits and number of days (Length of Stay-LOS). This will also be summarised for each contact type (asthma-exacerbations, other healthcare contact).

4.9. Risk Benefit Analyses

A forest plot will be produced to display efficacy and safety data from analyses in adjacent panels using Full Analysis Set.

The efficacy results will include primary endpoint (and its associated endpoint), i.e. clinically significant exacerbations (and exacerbations requiring hospitalisation and/or ED visit). The AE results will be obtained from the analyses as described in Section 4.6.2.1 for the following categories of AEs:

- On-treatment SAE
- Systemic Reactions
  - Allergic (Type 1 hypersensitivity) reactions
    - Anaphylaxis
  - Other systemic reactions
- Type III hypersensitivity/vasculitis
- Local injection site reactions

4.10. Analyses on Japan Subpopulation

A set of key study population, efficacy, safety, immunogenicity, PD and PK analyses will be repeated in the Japan subpopulations (as defined in Section 3, Analysis Sets). Details are provided in the OPS.

4.11. Interim Analyses

There will be one unblinded interim analysis for futility. Periodic review of safety data by an independent data monitoring committee (IDMC) will also be performed. Other than the emergency unblinding procedures described in the protocol, all personnel having direct responsibility for the conduct of the study will remain blinded to treatment groups for all data until the database is frozen.

4.11.1. IDMC Safety Review

IDMC will periodically review unblinded safety data from the three Phase III studies in the severe asthma program: 206713, 213744 (this study) and 206785, in accordance with the IDMC Charter. IDMC will also review safety data from study 212895, an open-label extension study including participants who were previously enrolled in study 206713 or 213744 when sufficient data is collected.

The IDMC will review all safety data, including AEs and serious adverse events (SAEs) and adverse events of special interest (AESI), laboratory parameters, including

haematological and clinical chemistry parameters and ECG assessments from the three studies for identification of any potential safety signals. The safety data analyses for the IDMC reviews will be performed by an independent Statistical Data Analysis Centre (SDAC).

4.11.2. Unblinded Interim Analysis for Futility

An unblinded interim analysis for futility will be conducted by an independent SDAC in conjunction with an IDMC to maintain study integrity.

The futility analysis will evaluate efficacy based on the primary endpoint of annualised rate of clinically significant exacerbations using interim data from Phase III studies 206713 and 213744 (this study) when approximately 675 participants are randomised across both studies. The stopping rule is binding, i.e. if the stopping criteria is met then the recommendation will be to stop, conditional on the IDMC deeming that there is no delayed onset of clinical efficacy. Should it be judged that there is delayed onset then this may invalidate an assumption of the interim analysis that the pre-interim data is reflective of post-interim data which could result in inflation of type 2 error. In such a situation, the IDMC will use their expert judgment in determining their recommendation.

Recruitment into the study will continue whilst the futility analysis is taking place. Any communication to the sites regarding the decision will only take place if a decision to stop the study is made. Should the studies be stopped, all on-going participants will complete their follow-up period but will not receive any further doses whilst no further participants will be recruited into the study.

The full details of the process are included in IDMC Charter.

4.11.2.1. Decision Rule

The interim analysis will be based on the predictive probability of meeting the end of study (program) success criteria (defined as statistical significance at a two-sided 5% alpha level in **both** studies 206713 and 213744). Should the predictive probability of success be less than or equal to 0.25 then the studies will be stopped for futility.

The futility rule:

Futility	**Continue**
Predictive probability (statistical significance two-sided 5%) in **both** 206713 & 213744) ≤ 0.25	Predictive probability (statistical significance two-sided 5%) in **both** 206713 & 213744) > 0.25

4.11.2.2. Methodology

Predictive probability of success will be used to determine the decision of futility or continue. The methodology involves predicting the remainder of the data on the primary endpoint for participants that have not yet completed or yet to be randomised into the study. The primary analysis is then performed separately for each study on this "complete" dataset, i.e. comprising of observed pre-interim data and predicted post-interim data. The success criteria is applied at this stage. To account for uncertainty attached to parameters at the interim, and therefore uncertainty in the predicted remaining

data (due to the limited data), this step is performed 1000s of times. The proportion of iterations that meet the success criteria (statistical significance in both studies) gives the predictive probability of success. If this is low (≤0.25), the studies will stop for futility Specific steps on the methodology are given below.

1. Data on the primary endpoint (number of clinically significant exacerbations) will be pooled across the two pivotal studies (206713, 213744) for the purposes of predicting post-interim data. Pooling allows for a more precise estimate of the overall treatment effect resulting in improved operating characteristics. Since these are replicate studies the pooling is deemed appropriate. Participants with at least one month of time in the study since randomisation will be included in the interim analysis (the negative binomial model accounts for varying follow-up time across participants).
2. The primary analysis with pooled data across both studies will be fitted (plus an additional fixed term for study) in a Bayesian framework (non-informative priors on all model parameters). Posterior distributions for the β model parameters and k dispersion parameter will be obtained with 1000s of sets of samples (iterations) taken from these posterior distributions which will be shown in the steps below to be used to predict exacerbations in the post-interim period.
3. For each iteration the expected number of exacerbations pre and post-interim is calculated as $\hat{y}_{i,1}$ and $\hat{y}_{i,2}$, respectively, for each participant, i. The predictions for post-interim data will be based on the interim posterior distribution. To calculate $\hat{y}_{i,1}$ and $\hat{y}_{i,2}$, the steps are as follows:
    1. The design matrix (Z) is multiplied with the set of posterior β samples and then back-transformed (exponentiated) to give expected annualised exacerbation rate for each participant (μ_i) based on the interim data. Note: for participants yet to be randomised, and therefore without values observed for baseline covariates, bootstrapping from already randomised participants will be performed.
    2. The expected exacerbation rate for the pre-interim and post-interim periods are calculated by multiplying μ_i by the pre-interim and post-interim times in the study for the participant: $\hat{y}_{i,1} = \mu_i \times t_{i,1}$ and $\hat{y}_{i,2} = \mu_i \times t_{i,2}$.
    3. For the two periods (pre and post-interim), the number of exacerbations within each period is negative binomial. The distribution of one period conditional upon the other, within a participant, is also negative binomial [Keene, 2014]. The negative binomial parameters for the post-interim period are calculated for each participant and set of posteriors samples (iteration):

$$p_{i,2} = \frac{\frac{1}{k} + \hat{y}_{i,1}}{\frac{1}{k} + \hat{y}_{i,1} + \hat{y}_{i,2}}$$

$$k_{i,2} = k_1 + count_{i,1}$$

Where k_1 is the sampled dispersion parameter, $count_{i,1}$ is the number of exacerbations for participant *i* in period 1 (pre-interim), *i* is the participant and *j*=1,2 is the period (pre, post-interim).

Using these parameters, simulate a participant's number of clinically significant exacerbations for post-interim data for each set of posterior samples

4. The pre-interim observed data (one set) will be combined with each set of post-interim data (1000s of sets) to create 1000s of end of study datasets
    1. Each participant's exacerbation count will be the summation of pre-interim observed count (if the participant was randomised at least one month before the interim data cut) plus the post-interim simulated exacerbation count (if the participant did not complete before the interim).
    2. Each participant's length of time in the study will now be the assumed average length of time in the study, which is set at 0.86 years.
5. The primary analysis model is applied to each iteration (dataset), each study separately. The p-value for the treatment effect (rate ratio) will be calculated. For each iteration, if the success criteria (statistical significance at 5% two-sided level for both studies) is met then the iteration is marked as success (flag as 1), or if not then fail (flag as 0).
6. The mean of these success flags in step 7 is calculated to give the predictive probability of success.
7. If the predictive probability of success is ≤0.25 then the futility criteria has been met.

4.11.2.3. Timing and Operating Characteristics

The proposed timing of the futility analysis is when approximately 675 participants have been randomised across the studies. At this time it is estimated that approximately 200 participants will have completed the studies and 500 received both doses (i.e. at least 6 months worth of data). The median follow-up time in the interim analysis is estimated to be 9 months with the information fraction for the primary endpoint estimated to be 60%, where information fraction is calculated as:

$$Information\ fraction = \frac{\sum_{i=1}^{n(interim)} length\ of\ time\ in\ study\ \boldsymbol{at\ interim}_i}{\sum_{i=1}^{750} length\ of\ time\ expected\ i\boldsymbol{n\ complete\ study}_i}$$

Table 5 shows operating characteristics of the futility analysis for a range assumed true treatment effects when approximately 725 participants have been randomised (proposed interim timing). Operating characteristics were obtained by simulating 5,000 studies and following the steps in Section 4.11.2.2 for each simulated study. Operating characteristics are obtained from the aggregate of these simulations.

As this is a futility analysis and there is no opportunity to stop for efficacy the type 1 error (calculated under the null hypothesis of assumed rate ratio = 1) is controlled well below the 5% level. The power of each study is approximately 99%, compared with >99% in the scenario where there is no futility analysis (as described in the protocol). The

expected observed rate ratio at the interim to trigger futility is expected to be approximately 0.70.

Table 5 Operating Characteristics of Futility Analysis

Assumed treatment effect (rate ratio depemokimab vs. placebo)	Probability of success (statistical significance in both studies)	Power[1]: 206713	Power[1]: 213744	Probability of futility
1	<0.01	<0.01	<0.01	0.98
0.9	0.01	0.04	0.02	0.94
0.8	0.08	0.18	0.13	0.76
0.7	0.37	0.50	0.44	0.42
0.6	0.78	0.85	0.82	0.11
0.5	0.98	0.98	0.98	0.01

[1] at two-sided 5% significance level for end of study test and incorporating the possibility of futility

4.11.2.4. Outputs

- An interim analysis-specific output presenting the predicted probability of success at the interim
- An interim analysis-specific output presenting model-adjusted annualised exacerbation rate ratio for depemokimab compared to placebo by time period (< 3 months since randomisation, 3 – 6, 6 – 9, 9 – 12)
- Kaplan-Meier plot of time to first clinically significant exacerbation
- Primary analysis summary table for each study. The primary analysis will be conducted on the interim data and provide model-adjusted estimates as a supportive output.
- Summary of Subject Disposition and Reasons for Study Withdrawal
- Summary of Demographic Characteristics
- Summary of Time in Study

4.11.2.5. Decision Making

The outputs from the interim analysis will be forwarded from the SDAC to the IDMC. As the stopping rule is binding, the decision will be communicated from the SDAC to the IDMC and then to GSK following agreement from the IDMC.

4.12. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol amendment 2 (Dated: 08-APR-2022) and its rationale are summarised as below.

Substantial validation work has been conducted on the ADSD/ANSD PRO measures since the original protocol and SAP were finalised. These measures will provide additional treatment benefit information and could be included in the label for treatment

decision making. Consequently, and following additional regulatory agency feedback, ADSD/ANSD change from baseline at week 52 endpoints have been added as secondary endpoints and into the hierarchy. In addition, ADSD and ANSD responders have been added as other endpoints.

5. SAMPLE SIZE DETERMINATION

Approximately 540 participants with severe uncontrolled asthma with an eosinophilic phenotype will be screened to ensure the randomisation of 375 participants in a 2:1 ratio to GSK3511294 (n=250) and matching placebo (n=125).

5.1. Sample Size Assumptions

A sample size of 375 participants (2:1 GSK3511294 to placebo allocation ratio) is based on sufficient power to conclude superiority on primary and key secondary endpoints.

5.1.1. Primary Endpoint

The assumed true annualised rate of exacerbations in the placebo arm is 1.18. Based on an assumed true treatment difference of a 50% reduction in annualised exacerbation rate between GSK3511294 + SoC and placebo + SoC, a sample size of 375 randomised participants (250 to GSK3511294, 125 to placebo) will provide 99% power for the primary endpoint at a 5% two-sided significance level [PASS, 2020].

The assumptions for the placebo rate and treatment effect are median values from an elicitation exercise which used Phase 3 anti-IL-5/5R historical data (~50% reduction in exacerbations) and expert opinion. The sample size is based also on an assumption of 0.8 for the dispersion parameter which was observed in two mepolizumab studies [Pavord, 2012; Ortega, 2014]. It was assumed that 14% of participant-years data will be missing due to study withdrawal, which is also consistent with mepolizumab studies.

Based on the assumptions above, the minimum observed treatment difference estimated to result in significance at the 5% two-sided significance level is a 27% reduction in exacerbations for GSK3511294 + SoC compared with placebo + SoC (rate ratio of 0.73).

5.1.2. Secondary Endpoints

Table 6 describes the assumptions and power values for two key secondary endpoints. The assumptions are obtained from the Phase 3 mepolizumab studies [Pavord, 2012; Ortega, 2014; Chupp, 2017].

Table 6 Power Calculations for Key Secondary Endpoints

Endpoint	Assumed treatment difference (GSK3511294 + SoC vs. placebo + SoC)	Standard deviation	Power
Change from baseline in SGRQ total score at Week 52	-7	17	96%
Change from baseline in ACQ-5 score at Week 52	-0.35	1.1	83%

5.2. Sample Size Sensitivity

The sample size and power calculations are based on assumptions about the true values for parameters. The power of the study is dependent on changes in these assumptions, in particular the assumed annualised exacerbation rates. Table 7 illustrates how changes in assumptions for two parameters (placebo + SoC annualised exacerbation rate and treatment effect) affect the power.

Table 7 Estimates of Power for Assumed Placebo + SoC Exacerbation Rate and Assumed Percent Reduction with GSK3511294 + SoC Compared with Placebo + SoC

Percent reduction in annualised exacerbation rate with GSK3511294 + SoC vs. placebo + SoC	Placebo + SoC annualised exacerbation rate			
	1.0	1.1	**1.18**	1.3
30%	61	63	65	67
40%	88	90	91	92
50%	98	99	**99**	99

5.3. Sample Size Re-estimation or Adjustment

There will be no sample size re-estimation.

There is a possibility for randomising greater than 375 participants in the study. This is due to local country requests or requirements, for example, the local health authority specifying a minimum number to be enrolled. The primary analysis and clinical study report (CSR) will be based on the initial target enrolment. If the study target enrolment is reached before a local country enrolment requirement is met, then recruitment in that country may continue. Participants from those countries, who have already been enrolled at the time of reaching the target enrolment, will be included in the primary analysis. All data (pre- and post-target enrolment) will be analysed together but reported later in a supplement to the study report. Inferences will be drawn on the original study report based on the target enrolment.

6. SUPPORTING DOCUMENTATION

6.1. Early PK Access Key Activities

Designated representative(s) may be unblinded for performing population PK, PKPD dataset preparation and draft PK, PKPD model development using scrambled (random reassignment of subject identification numbers) PK, PKPD unblinded datasets. The PK and PKPD datasets will include information on PK concentration, actual dosing information, demographics (including race and ethnicity), vital signs, concomitant medications, antidrug antibodies, biomarkers (e.g. eosinophils and IL5 concentration) and laboratory information. No information on adverse event and efficacy will be included.

6.2. Appendix 1 Abbreviations and Trademarks

6.2.1. List of Abbreviations

Abbreviation	Description
ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
ADSD	Asthma Daily Symptom Diary
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANSD	Asthma Nightly Symptom Diary
Anti-IL-5	Anti-Interleukin-5
BP	Blood pressure
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPMS	Clinical Pharmacology Modeling and Simulation
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case report form
ED	Emergency Department
eDiary	Electronic diary
FAS	Full Analysis Set
FAS	Full Analysis Set
FEV1	Forced expiratory volume in 1 second
GSK	GlaxoSmithKline
HRQoL	health-related quality of life
ICS	Inhaled corticosteroids

Abbreviation	Description
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IL-5	Interleukin-5
IM	Intramuscular
IV	Intravenous
KR method	Kenward and Roger method
LOS	Length of Stay
LS Mean	Adjusted mean for the treatment group
LS Mean Change	Adjusted mean change from baseline for the treatment group
MAR	Missing at Random
Max	Maximum
MedDRA	Medicinal dictionary for regulatory activities
Mg	Milligram
Min	Minimum
MMRM	Mixed Models Repeated Measures
MNAR	Missing Not at Random
NAb	Neutralising antibody
NHANES	National Health and Nutrition Examination Survey
OCS	Oral corticosteroids
OPS	Output and Programming Specification
OR	Odds ratio
PD	Pharmacodynamics
PEF	Peak expiratory flow

Abbreviation	Description
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PRO	Patient-reported outcomes
PROMIS	Patient-reported outcomes measurement information system
PT	Preferred Term
QTcF	QTc corrected by Fridericia's formula
RAP	Reporting and Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SGRQ	St George's Respiratory Questionnaire
SNOT-22	Sino-nasal Outcomes Test-22
SoC	Standard of care
SOC	System Organ Class

6.2.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

7. REFERENCES

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Summary of SAP changes (206713 and 213744)

Version 1.0 to 2.0	
Section 1.1.2 Estimand	Updated intercurrent event strategy for change in maintenance therapy
Section 3 Analysis Sets	• Updated text related to enrolled, randomised, full analysis set, and safety population • (206713 only) Added China subpopulation • (213744 only) Added Japan subpopulation
Section 4.3.2	Updated model checking method
Section 4.4.9	Removed statistical analysis of PGIP/ PGI-C endpoints
Section 4.4.10 ADSD/ANSD	Added study 217640
Section 4.5.2	Updated imputation method for nondetectable blood eosinophil values of 0 GI/L, or results below the limit of quantification
Section 4.6.3.3	Adding two visits for ECG reporting and modified wording for categories to be reported
Section 4.9	Added unblinded interim analysis for futility and blinded analysis for validation of questionaries
Section 4.10	Removed that Table of 'Changes to Protocol Defined Analyses'
Section 4.4.15	Added a summary of systemic corticosteroids use associated with clinically significant exacerbations
Version 2.0 to 3.0	
Section 1.1.1 Endpoints and Section 2.1 Multiplicity Adjustment	ADSD and ANSD elevated in the hierarchy as secondary endpoints
Section 1.1.2 Estimands	• Updated for the endpoints with descriptive summaries, changed from 'while on treatment strategy' to 'hypothetical strategy' • Removed safety endpoints from the table
Section 3	• Updated FAS and Safety analysis sets • Added FAS-modified and Safety modifitied analysis sets
Section 4.1.2 Baseline Definition	Changed from 'Day -7 to Day 1' to 'Day -6 to Day 1'
Section 4.2.2, 4.3.2, 4.4	Main Analytical Approach, removed the covariate of ' baseline maintenance OCS therapy (OCS vs. no OCS)' from the analysis model
Section 4.2.3.2	Removed condition for performing tipping point sensitivity analysis
Section 4.4.10.2	Added analysis for responder based ADSD/ANSD
Section 4.4.13	Added a PEF plot
Section 4.4.15	Removed the sentences regarding summary of number of days with systemic corticosteroids (including OCS, IV and IM) use
Section 4.9	Added the section to describe the Risk Benefit forest plot
Section 4.3.2, 4.4.3, 4.4.10	Added suggestion for how to exclude timepoints from analysis when the model does not converge
Section 4.10	(206713 only) Added clarification for analyses on China subpopulation
Section 4.1.1	Added clarification for covaiates
Section 4.3.3	Added condition for performing analysis
Version 2.0 to 3.0 (213744 only)	
Section 3	Modified Screened population
Section 4.1.4 and Section 4.2 & 4.3	Added subgroup definitions and subgroup analyses
Section 4.2.3.2	Added a condition for performing Tipping Point analysis
Section 4.5.2	Added summary of AE by subgroups