Supplementary Appendix

Supplement to: 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 appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

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All authors contributed to data interpretation. All authors contributed to the drafting of the manuscript or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Supplementary Study Design

The following important changes were made to the protocol after study registration:

- Electrocardiogram assessments were added at Week 2 and Week 28 clinic visits
- The requirement for documentation of airway reversibility or airway hyperresponsivenesswas updated so as to specify that it should be documented for the 24 months prior to Visit 2; the original protocol specified that airway reversibility or airway hyperresponsiveness should be documented for only 12 months prior to Visit 2
- Blinded interim analysis was included for futility
- COVID-19 monoclonal antibodies were added as authorized treatments

Spirometry was measured via a centrally provided spirometer with results sent directly to the provider. Patient-reported outcomes were entered on patient handheld devices and relayed to the central provider. The rest of the data were collected at study sites and recorded by site staff in electronic case report forms. Medical evaluation of patient's asthma could take place via telemedicine if visits to a site/home were not feasible.

Standard of care was a patient's existing maintenance asthma therapy, consisting of ICS plus ≥1 additional controller (e.g., long-acting β-agonists or long-acting muscarinic antagonists, with or without maintenance OCS) and excluding biologics. Adherence to standard of care therapies was not specifically recorded, but standard of care therapies were provided by the study sponsor in China and Japan in line with local requirements.

The dose of depemokimab 100 mg at Week 0 and Week 26 was selected based on the eosinophil endpoint from the Phase I study in patients with mild-to-moderate asthma and a blood eosinophil count ≥200 cells/μL at screening.[1] This study was designed to collect robust blood eosinophil pharmacology data to inform dose selection using model-informed drug development principles. Two mepolizumab Phase III studies demonstrated that blood eosinophil reduction could be used as a

predictor of efficacy among patients with severe asthma with an eosinophilic phenotype. In these trials, the annualized exacerbation rate consistently reduced by approximately 50%, with associated reductions in blood eosinophils (84% in the MENSA trial; 78% in the MUSCA trial) compared with placebo.[2,3]

Supplementary Eligibility Criteria

Participants were eligible to be included in the studies if they met all of the following criteria:

1. Adults and adolescents ≥12 years of age, at the time of signing the informed consent/assent.
2. Documented physician diagnosis of asthma for ≥2 years that meets the National Heart, Lung, and Blood Institute (NHLBI) guidelines[4] or GINA 2020 guidelines[5] with each of:
    a) A confirmed (or high likelihood of having) eosinophilic phenotype (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 an elevated peripheral blood eosinophil count of ≥150 cells/µL at Screening Visit 1 that is related to asthma).
    b) A history of ≥2 exacerbations requiring treatment with SCS (intramuscular, intravenous or oral), in the 12 months prior to Visit 1, despite the use of medium to high-dose ICS; for participants receiving maintenance corticosteroids, the treatment for the exacerbations must have been a two-fold dose increase or greater.
3. Persistent airflow obstruction indicated by:
    a) Pre-bronchodilator FEV_1 <80% predicted (NHANES III) recorded at Visit 1 (for participants ≥18 years of age at Visit 1).
    b) Pre-bronchodilator FEV_1 <90% predicted (NHANES III) recorded at Visit 1 OR FEV_1:FVC ratio <0.8 recorded at Visit 1 (for participants 12–17 years of age at Visit 1).
4. 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 µg fluticasone proprionate hydrofluoroalkane daily, or clinically comparable.[5] Participants treated with medium-dose ICS will also need to be treated with LABA to qualify for inclusion.
5. Receiving treatment with at least one additional controller medication, besides ICS, for ≥3 months (LABA, LAMA, leukotriene receptor antagonist, or theophylline).
6. Both male and female participants were eligible. Female participants were eligible if they met the following criteria:
    a) A woman of non-childbearing potential (WONCBP) OR of childbearing potential and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in from ≥14 days prior to the first dose of study intervention until ≥30 weeks after the last administered dose of study intervention.

b) WOCBP with 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.
c) Contraceptive use by women should be consistent with local regulations regarding the methods of contraception.
d) The investigator should evaluate the potential for contraceptive method failure and 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.

7. Capable of giving signed informed consent/assent.
8. In France, a participant will be eligible for inclusion in these studies only if either affiliated to or a beneficiary of a social security category.

Participants were excluded if they met any of the following criteria:

1. 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. Presence of other conditions that could lead to elevated eosinophils such as hyper-eosinophilic syndromes including (but not limited to) eosinophilic granulomatosis with polyangiitis or eosinophilic esophagitis.
3. A known, pre-existing parasitic infestation within 6 months prior to Visit 1.
4. A known immunodeficiency (e.g. human immunodeficiency virus), other than that explained by the use of corticosteroids taken as therapy for asthma.
5. A current malignancy or previous history of cancer in remission for less than 12 months prior to screening (participants that had localized carcinoma of the skin which was resected for cure will not be excluded).
6. Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice. 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. Presence of known, preexisting, clinically significant cardiac, endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.
8. 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. Participants that, according to the investigator's medical judgment, are likely to have active COVID-19 infection would be excluded. Participants with known COVID-19 positive contacts within the past 14 days would be excluded for ≥14 days following the exposure during which the participant should remain symptom-free.
10. Have received monoclonal antibodies targeting IL-5/5 receptors (e.g. mepolizumab, reslizumab, or benralizumab) within 12 months prior to Visit 1 or who have a previous documented failure with anti-IL-5/receptor therapy.
11. Have received other monoclonal antibodies in the treatment of asthma (e.g. omalizumab or dupilumab) within 130 days prior to Visit 1.
12. Have received other monoclonal antibodies not used for the treatment of asthma within five half-lives of Visit 1. Authorized treatments for COVID-19 are permitted.
13. 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).
14. Previously participated in any study with mepolizumab, reslizumab, or benralizumab and received study intervention (including placebo) within 12 months prior to Visit 1.
15. Electrocardiogram (ECG) assessment of 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.
16. 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 ≥6 months prior to Visit 1.
17. History (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1.
18. Presence of allergy/intolerance to the excipients of depemokimab or any monoclonal antibody or biologic.
19. Participants who are pregnant or breastfeeding. Participants should not be enrolled if they plan to become pregnant during the time of study participation.

20. Known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations.

Supplementary Statistical Methods

A sample size of 375 patients for each replicate trial is based on sufficient power in each trial to conclude superiority on primary and key secondary endpoints. The assumed true annualized rate of exacerbations in the placebo arm was 1.18. Based on an assumed true treatment difference of a 50% reduction in annualized exacerbation rate between depemokimab and placebo, this sample size provided 99% power for the primary endpoint at a 5% two-sided significance level.[6] The assumed treatment difference for change from baseline to SGRQ total score at Week 52 was -7.0 (standard deviation [SD]: 17) and change from baseline in ACQ-5 at Week 52 was -0.35 (SD: 1.1), giving 96% and 83% power, respectively. These assumptions were obtained from Phase III mepolizumab studies.[2,3,7]

There was one unblinded interim analysis for futility when approximately 675 patients were randomized across both studies and periodic reviews of safety data by an independent data monitoring committee were performed.

Change from baseline to Week 52 in SGRQ, ACQ-5, ANSD and ADSD mean scores and prebronchodilator FEV_1, were analyzed using mixed models repeated measures models with covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, ≥4), geographical region, baseline SGRQ total score (for SGRQ analysis), ACQ-5 score (for ACQ-5 analysis), ANSD score (for ANSD analysis), ADSD score (for ADSD analysis), prebronchodilator FEV_1 (for prebronchodilator FEV_1 analysis), baseline prebronchodilator percent predicted FEV_1, visit, visit by baseline SGRQ total score (for SGRQ analysis), by baseline ACQ-5 score (for ACQ-5 analysis), by baseline ANSD score (for ANSD analysis), by baseline ADSD score (for ADSD analysis) or by baseline prebronchodilator FEV_1 (for prebronchodilator FEV_1 analysis), and visit by treatment group. Subgroup analyses were performed using a generalized linear model assuming a negative binomial distribution and covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, ≥4), geographical region, sex baseline pre-bronchodilator percent predicted FEV_1, study (SWIFT-1 or

SWIFT-2), subgroup and subgroup by treatment group. Exacerbations requiring hospitalization and/or ER visit were analyzed using a generalized linear model assuming a negative binomial distribution; annualized rate was only analyzed if ≥20 such exacerbations occurred during the study. Time to first exacerbation was estimated using Cox's proportional hazards model with covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, ≥4), geographical region and baseline pre-bronchodilator percent predicted FEV_1. The proportional hazards assumption was examined by obtaining the Kaplan–Meier estimates of the survival function S(t) over time separately for each treatment group. In addition, a ln {-ln[S(t)]} plot was produced (not shown). For all statistical analyses where the covariate of exacerbation history is included in the modelling, patients with exacerbation history <2 will be included in the category of '2'. Where the covariate of baseline pre-bronchodilator percent predicted FEV_1 is included, screening pre-bronchodilator percent predicted FEV_1 will be used if the baseline value is missing. If both screening and baseline pre-bronchodilator FEV_1 are missing, a missing value will be assigned for this covariate. Details on analysis of other pre-specified endpoints (**Table S1**) are described in the statistical analysis plans for both studies, which are available with the full text of this article at NEJM.org.For patients that discontinued study intervention due to reasons related to the COVID-19 pandemic, the observed data for the period following this intercurrent event were excluded from the analysis. Data for this period following the intercurrent event were assumed "missing at random" (MAR; based on all data included in the analysis under the current estimand strategy). For patients that withdrew from the study, preventing assessment of the primary endpoint, the data for the period following withdrawal were assumed MAR (based on all data included in the analysis under the current estimand strategy). Tipping point sensitivity analyses were conducted to assess the robustness in the treatment effect and conclusion in the main analytical approach when departing from the missing at random assumption. Subjects who withdrew from study early had 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 were based on increases relative to the estimated rates (delta) obtained within each arm under the MAR assumption. The imputed exacerbation rates varied independently for the depemokimab and placebo arms and included scenarios where patients in the depemokimab arm have worse outcomes following early withdrawal from the study than patients in the placebo arm. The tipping point imputation method was based on pattern mixture models.[8] The results from the analyses of each sample are combined using Rubin's method. Results from these sensitivity analyses for the primary endpoint are presented in **Table S24**.

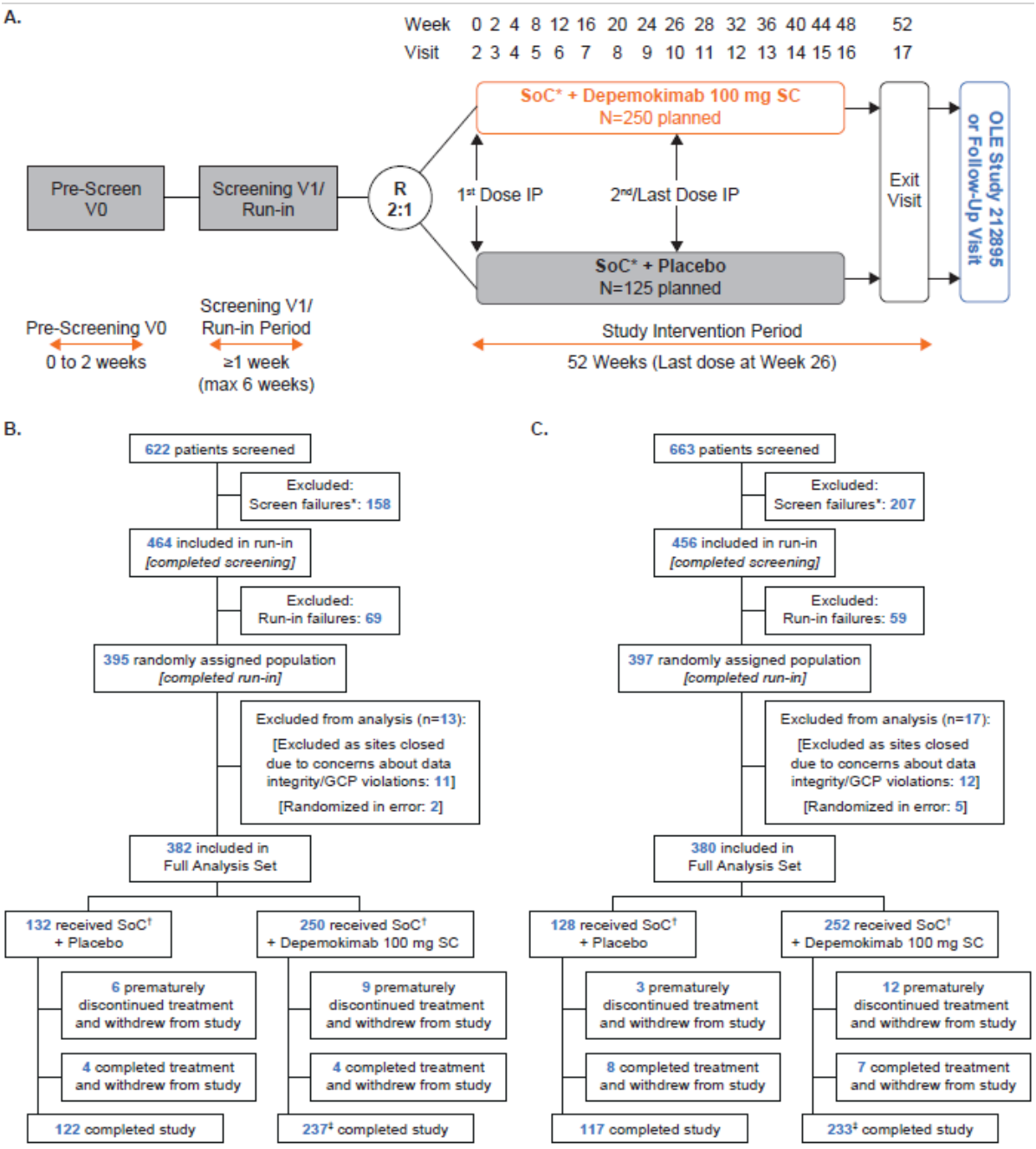
There was no hierarchy or multiplicity adjustment in the pooled analysis. Also, an additional term for study was used in the pooled analysis model.

Supplementary Post Hoc Subgroup Analysis Results

In a post hoc subgroup analysis of patients enrolled in Poland, there was a 1% difference between treatment groups for exacerbations (**Figure S6**), with an annualized exacerbation rate (95% CI) of 0.33 (0.22, 0.51) for depemokimab and 0.34 (0.18, 0.62) for placebo (there was a 57% difference between depemokimab [0.55 (0.47, 0.66) and placebo [1.30 (1.07, 1.58)] in the rest of the world excluding Poland). Further, in the Poland subgroup, the change from baseline in SGRQ at Week 52 (95% CI) was -8.10 (-11.59, -4.61) for depemokimab and -12.95 (-17.84, -8.06) for placebo (treatment difference [95% CI]: 4.85 [-1.09, 10.79]); for the rest of the world excluding Poland, change from baseline in SGRQ was -15.26 (-16.91, -13.62) for depemokimab and -10.56 (-12.84, -8.28) for placebo (treatment difference [95% CI]: -4.70 [-7.51, -1.90]). In post hoc analyses, depemokimab-treated patients with poor asthma control at baseline (ACQ-5 score ≥1.5) demonstrated a reduction in annualized rate of exacerbations versus those treated with placebo (**Figure S6**).

Supplementary Figures

Figure S1. (A) Study design and patient disposition for SWIFT-1/2, and CONSORT diagrams for (B) SWIFT-1 and (C) SWIFT-2



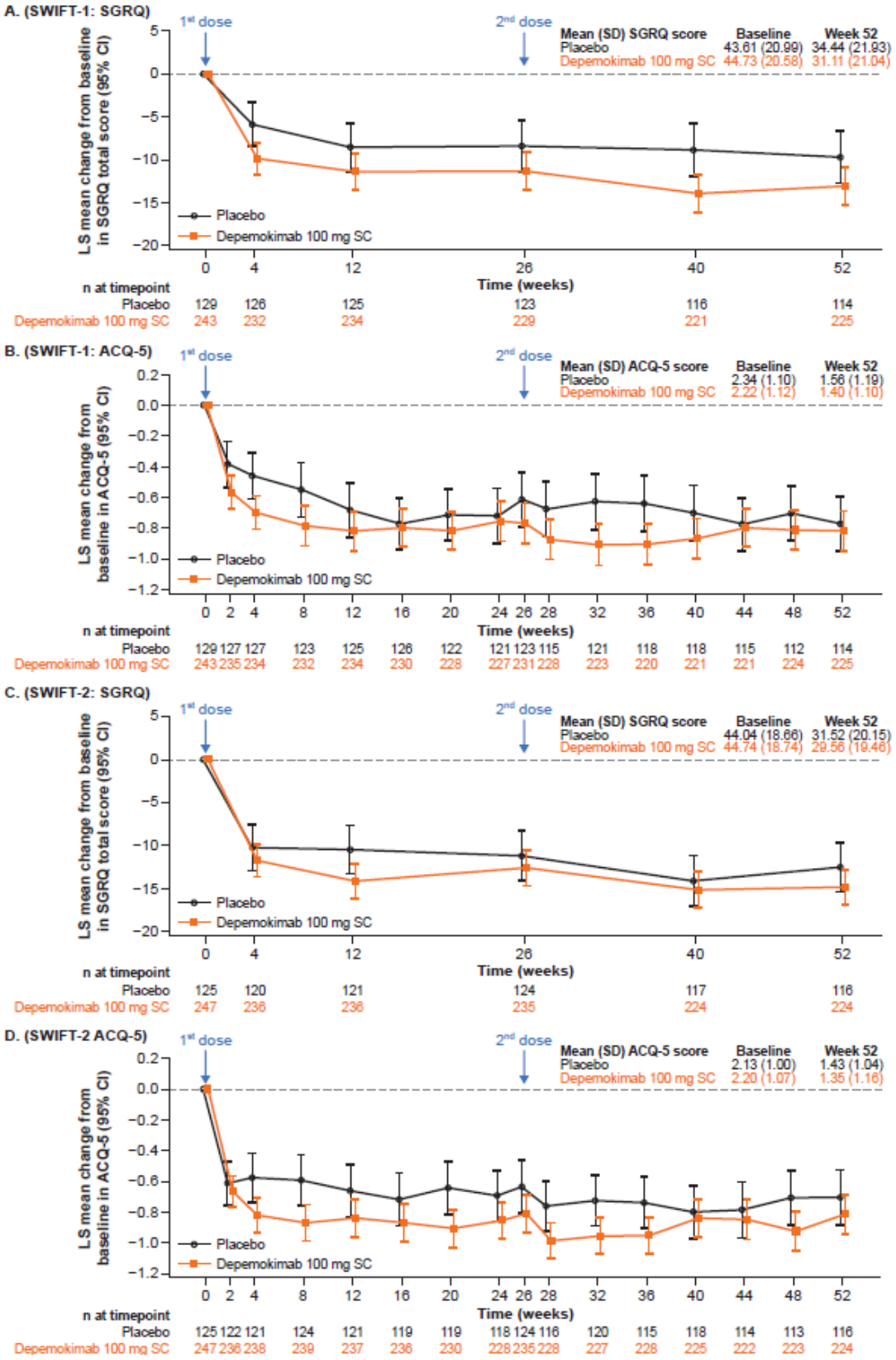
*The most common reason for screen failure was not meeting inclusion/exclusion criteria (142/158 patients in SWIFT-1 and 190/207 in SWIFT-2). Other reasons were loss to follow-up, physician decision, protocol deviation, study termination by sponsor, or withdrawal by subject.

[†]SoC medium- to high-dose ICS (add) plus additional controller. SoC asthma therapy to exclude biologics.

[‡]5 patients in SWIFT-1 and 1 patient in SWIFT-2 prematurely discontinued treatment but remained in study and completed study.

ICS, inhaled corticosteroids; GCP, good clinical practice; IP, investigational product; OLE, open-label extension; R, randomized; SC, subcutaneous; SoC, standard of care; V, visit.

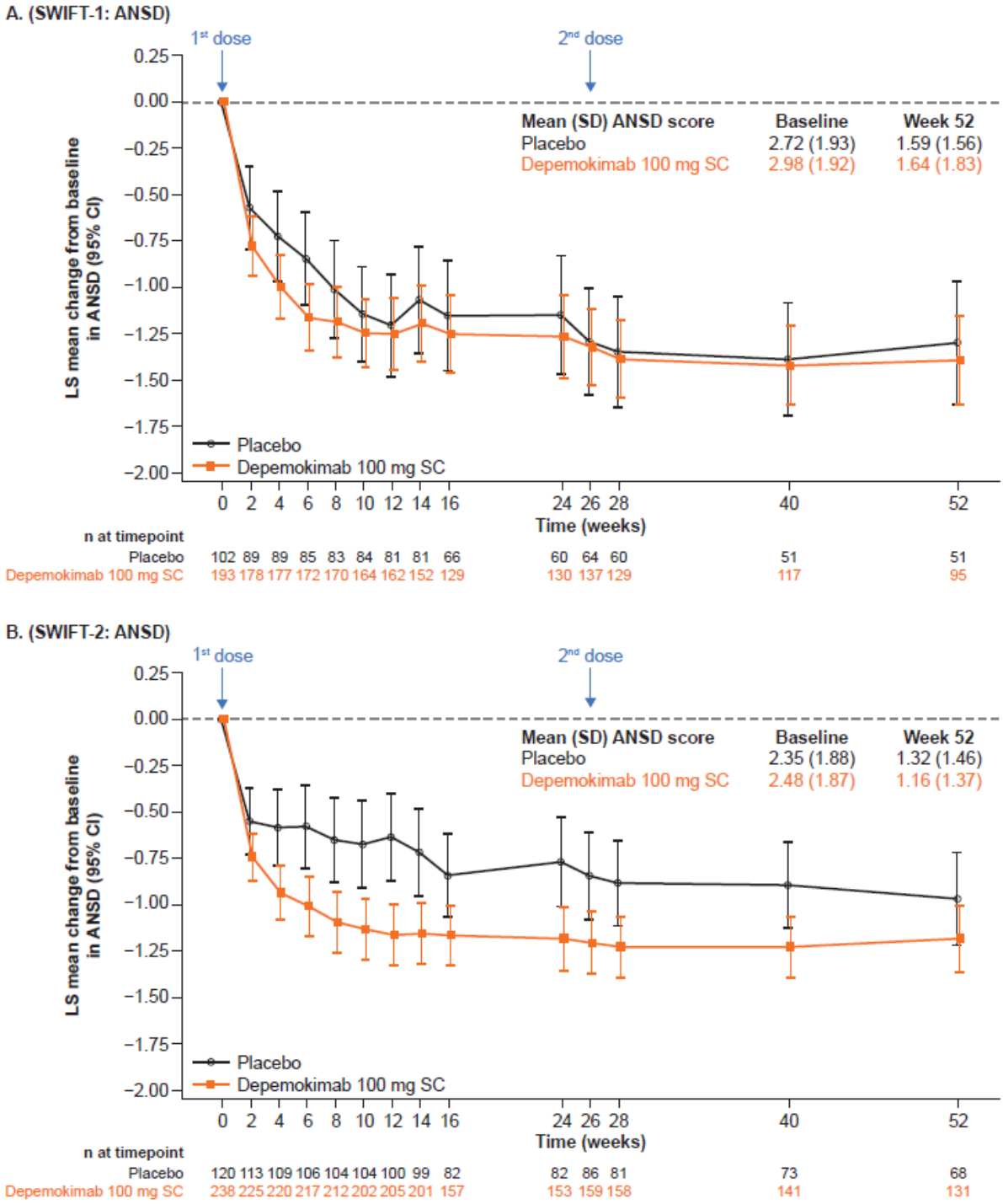
Figure S2. Change from baseline in SGRQ total score and ACQ-5 over time for (A and B) SWIFT-1 and (C and D) SWIFT-2



SGRQ: 0–100; higher scores indicate worse quality of life; within-patient MCID: -4.0.[9] ACQ-5: 0–6; higher scores indicate worse asthma control; within-patient MCID: -0.5.[10] Analyses performed using a repeated measures model with covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, ≥4), geographical region, baseline SGRQ total score (for SGRQ analysis) or ACQ-5 score (for ACQ-5 analysis), baseline prebronchodilator percent predicted FEV_1, visit, visit by baseline SGRQ total score (for SGRQ analysis) or by baseline ACQ-5 score (for ACQ-5 analysis), and visit by treatment group. CI widths have not been adjusted for multiplicity and should not be used for inferential purposes.

ACQ-5, Asthma Control Questionnaire-5; CI, confidence interval; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroids; LS, least squares; MCID, minimal clinically important difference; SC, subcutaneous; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

Figure S3. Change from baseline in ANSD weekly mean score for (A) SWIFT-1 and (B) SWIFT-2



ANSD score range is 0–10; higher scores indicates worse symptoms; within-patient MCID: -1.5.[11]

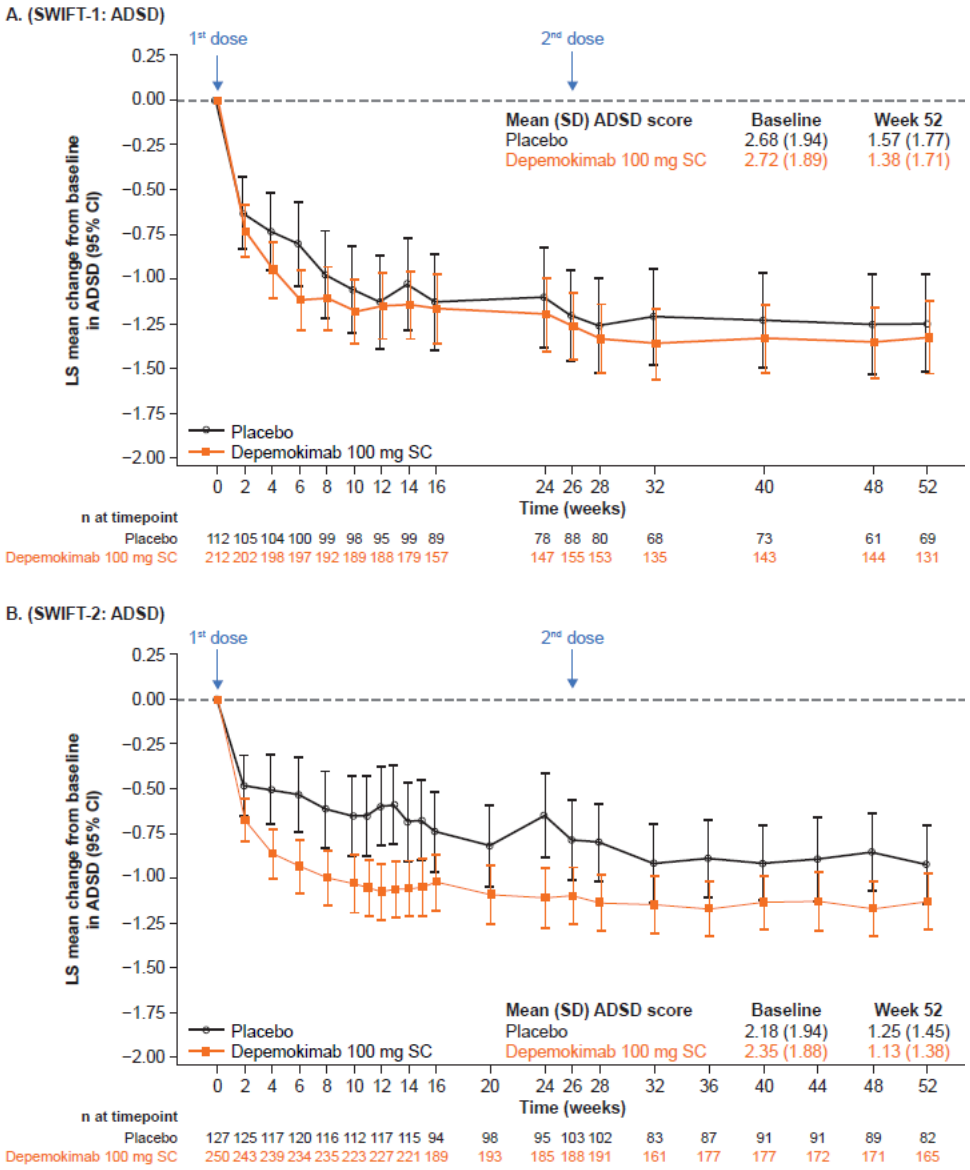
Analysis performed using a repeated measures model with covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, ≥4), geographical region, baseline ANSD

weekly mean score, baseline prebronchodilator percent predicted FEV_1, visit, visit by baseline ANSD weekly mean score and visit by treatment group. CI widths have not been adjusted for multiplicity and should not be used for inferential purposes.

Weeks 1, 3, 5, 7, 9, 11, 13, 15, 20, 32, 36, 44, and 48 have been excluded to allow for model convergence.

ANSD, asthma nightly symptom diary; CI, confidence interval; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroids; LS, least squares; MCID, minimal clinically important difference; SC, subcutaneous; SD, standard deviation.

Figure S4. Change from baseline in ADSD weekly mean score for (A) SWIFT-1 and (B) SWIFT-2



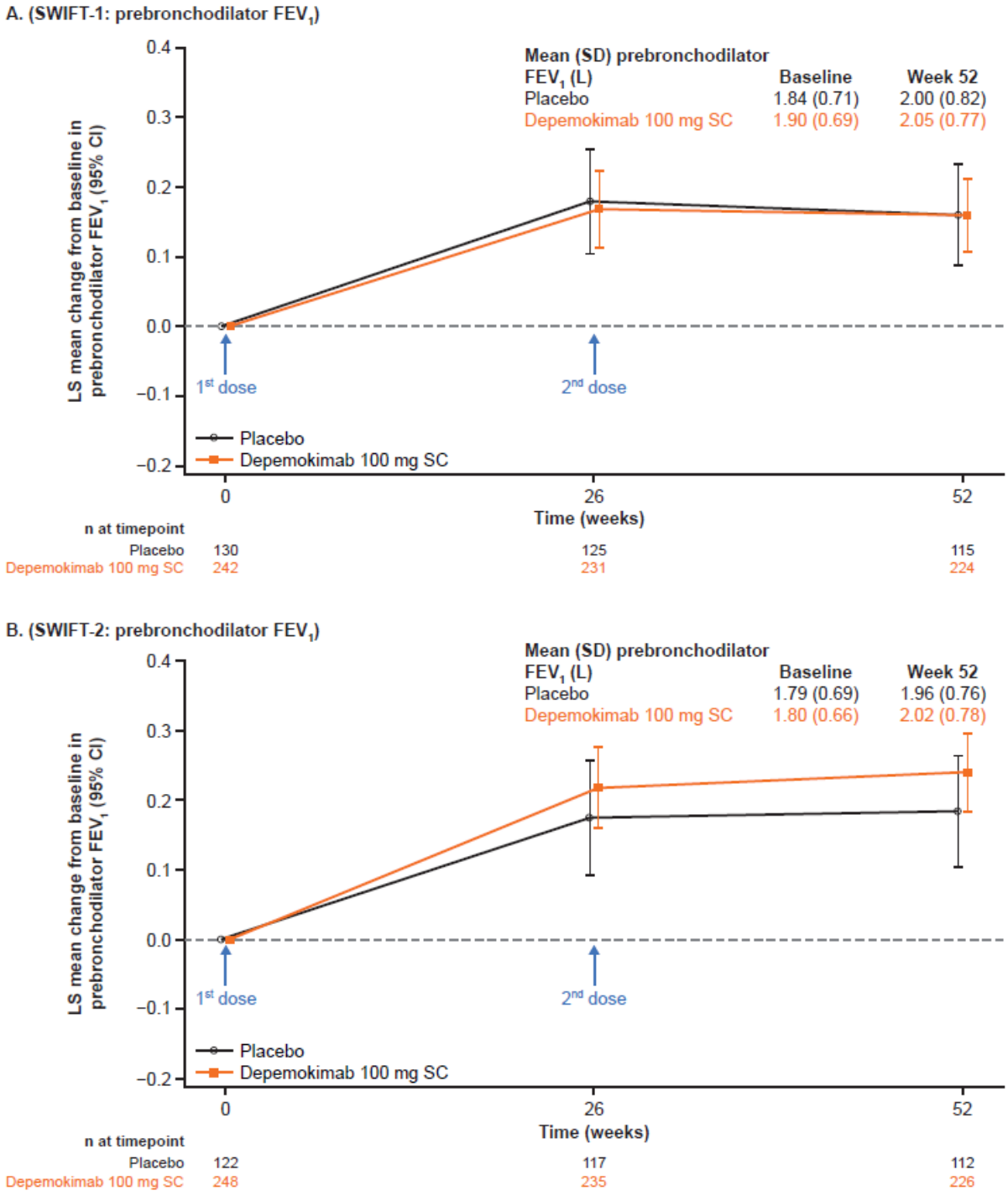
ADSD score range is 0–10; higher scores indicates worse symptoms; within-patient MCID: -1.2.[11]

Analyses performed using a repeated measures model with covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, ≥4), geographical region, baseline ADSD weekly mean score, baseline prebronchodilator percent predicted FEV_1, visit, visit by baseline ADSD weekly mean score, and visit by treatment group. CI widths have not been adjusted for multiplicity and should not be used for inferential purposes.

Weeks 1, 3, 5, 7, 8, 11, 13, 15, 20, 36, and 44 (SWIFT-1) and Weeks 1, 3, 5, 7, and 9 (SWIFT-2) have been excluded to allow for model convergence.

ADSD, asthma daily symptom diary; CI, confidence interval; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroids; LS, least squares; MCID, minimal clinically important difference; SC, subcutaneous; SD, standard deviation.

Figure S5. Change from baseline in prebronchodilator FEV_1 (L) in (A) SWIFT-1 and (B) SWIFT-2

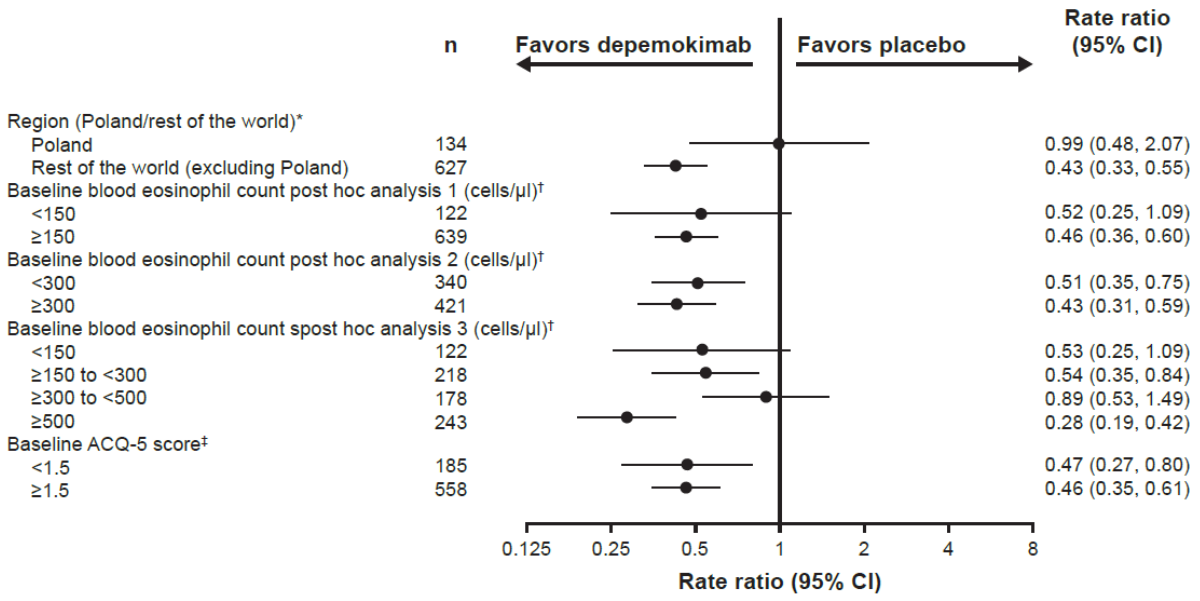


Analysis performed using a repeated measures model with covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, ≥4), geographical region, baseline

prebronchodilator FEV_1, visit, visit by baseline prebronchodilator FEV_1, and visit by treatment group. CI widths have not been adjusted for multiplicity and should not be used for inferential purposes.

CI, confidence interval; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroids; LS, least squares; SC, subcutaneous; SD, standard deviation.

Figure S6. Forest plot of primary endpoint by post hoc subgroup for pooled SWIFT-1/2 population



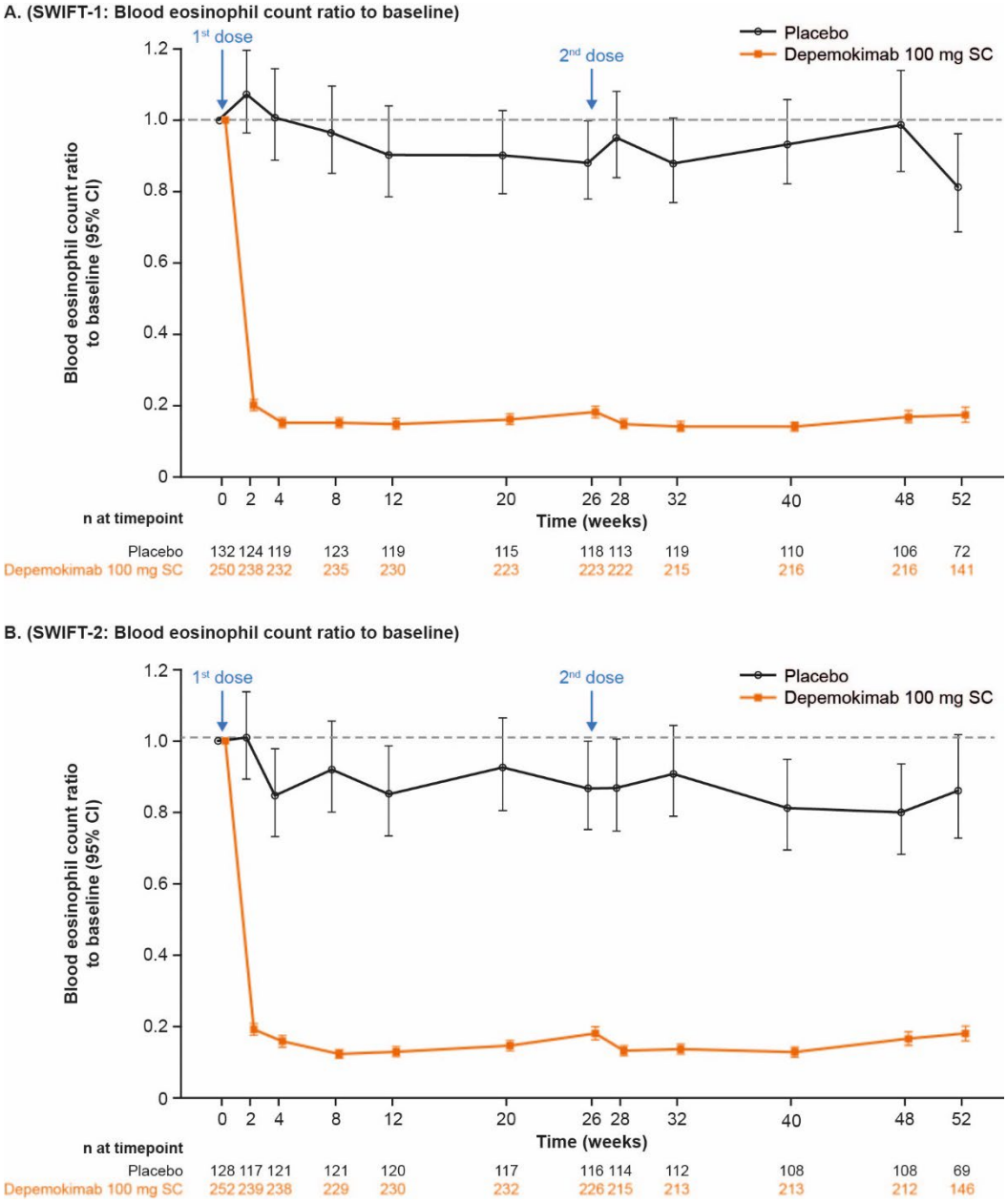
*Post hoc analyses were conducted to aid understanding of results from SWIFT-1 (for which results were available prior to SWIFT-2), which showed no significant treatment differences for secondary endpoint SGRQ, despite the significant effect seen for the primary endpoint. These exploratory analyses suggested that results in patients from Eastern Europe for the primary and secondary endpoints were not consistent with results from the rest of the world. We then explored further, using additional regional categories of Eastern Europe and rest of world excluding Eastern Europe and another of US, Western Europe, Eastern Europe, and rest of world excluding US, Western and Eastern Europe. These findings are consistent with results that have been reported for other biologics in Eastern Europe.[12,13] Subgroup analyses for Eastern Europe were therefore prespecified in the statistical analysis plan for SWIFT-2. Subsequently, upon review of the data for Eastern Europe in SWIFT-2, data from Poland were seen to be inconsistent with other European countries in both the primary and secondary endpoints in Poland. This observation was then seen to have been replicated across both studies. Further post hoc analyses were conducted to better understand the effect of Poland (n=134; the largest contributor to the Eastern Europe region) on results in the pooled dataset, in newly defined region subgroup: Poland and rest of world excluding Poland. These

analyses showed that there was a 1% treatment difference in exacerbation rates between treatment groups in Poland. Exacerbation rates in the depemokimab group in Poland were broadly consistent with the rate in other regions, whereas exacerbation rates in the placebo arm were not; [†]Post hoc subgroup analyses were conducted on different blood eosinophil count subgroups, in order to better understand the impact of different blood eosinophil count cut offs on exacerbation rate; [‡]A post hoc subgroup analysis of exacerbation rate by baseline ACQ-5 score was conducted to understand the impact of symptom control on outcomes.

Number of patients is the number of subjects with analyzable data for the two treatment groups of interest. Analysis performed using a generalized linear model assuming a negative binomial distribution and covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, ≥4), geographical region, sex baseline pre-bronchodilator percent predicted FEV_1, study (SWIFT-1 or SWIFT-2), subgroup and subgroup by treatment group. Only subgroup levels with ≥20 subjects were included in the statistical analysis. CI widths have not been adjusted for multiplicity and should not be used for inferential purposes.

ACQ-5, Asthma Control Questionnaire-5; CI, confidence intervals.

Figure S7. Ratio to baseline in adjusted geometric mean blood eosinophil count over study duration in (A) SWIFT-1 and (B) SWIFT-2



N=number of patients with analysable data at one or more timepoints. Analysis performed using a repeated measures model on loge transformed dependent variable with covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, ≥4), geographic region,

loge(baseline), visit, visit by loge(baseline) and visit by treatment group. CI widths have not been adjusted for multiplicity and should not be used for inferential purposes.

ICS, inhaled corticosteroids; SC, subcutaneous; SE, standard error.

Supplementary Tables

Table S1. Other pre-specified endpoints

Endpoint
Time to first exacerbation requiring hospitalization and/or ER visit
Change from baseline in PROMIS fatigue item scores
Change from baseline in SNOT-22 score
Patient-rated response to therapy during the 52-week period
Clinician-rated response to therapy during the 52-week period
PGI-S/PGI-C
Responders based on ANSD/ADSD
Change from baseline in 2-week mean number of occasions of rescue medication per day
Change from baseline in 2-week mean number of awakenings at night due to asthma symptoms requiring rescue medication use
Change from baseline in 2-week mean morning PEF
Change from baseline in weekly mean daily asthma symptom scores
Number of days with OCS

ADSD/ANSD, asthma daily/nightly symptom diary; ER, emergency room; OCS, oral corticosteroids; PEF, peak expiratory flow; PGI-S/C, Patient Global Impression of Asthma Severity/Change; PROMIS, Patient-Reported Outcomes Measurement Information System; SNOT-22, 22-Item SinoNasal Outcomes Test.

Table S2. Predefined hierarchy of endpoints

Position	Endpoint
1	Annualized rate of 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 prebronchodilator FEV_1 at Week 52
5	Change from baseline in ANSD at Week 52
6	Change from baseline in ADSD at Week 52
7	Annualized rate of exacerbations requiring hospitalization and/or ER visit over 52 weeks

ACQ-5, Asthma Control Questionnaire-5; ADSD, asthma daily symptom diary; ANSD, asthma nightly symptom diary; ER, emergency room; FEV_1, forced expiratory volume in one second; SGRQ, St George's Respiratory Questionnaire.

Table S3. Summary of asthma concomitant medications taken to prior to and during treatment by respiratory medication class group in ≥5% of patients in either treatment arm/study

Respiratory medication class	SWIFT-1		SWIFT-2	
	Placebo (N=132)	Depemokimab 100 mg SC (N=250)	Placebo (N=128)	Depemokimab 100 mg SC (N=252)
ICS, n (%)				
Prior to treatment	132 (100)	250 (100)	128 (100)	252 (100)
During treatment	132 (100)	250 (100)	128 (100)	252 (100)
Long-acting β_2 agonist, n (%)				
Prior to treatment	131 (>99)	247 (99)	126 (98)	249 (99)
During treatment	129 (98)	245 (98)	124 (97)	244 (97)
Leukotriene receptor antagonist, n (%)				
Prior to treatment	39 (30)	80 (32)	65 (51)	116 (46)
During treatment	34 (26)	77 (31)	62 (48)	109 (43)

SCS, n (%)				
Prior to treatment			46 (36)	93 (37)
During treatment	53 (40)	93 (37)	66 (52)	88 (35)
	68 (52)	83 (33)		
Long-acting anticholinergic, n (%)				
Prior to treatment	35 (27)	69 (28)	46 (36)	87 (35)
During treatment	33 (25)	66 (26)	48 (38)	81 (32)
Short-acting anticholinergic, n (%)				
Prior to treatment	17 (13)	31 (12)	12 (9)	23 (9)
During treatment	10 (8)	19 (8)	8 (6)	12 (5)
Antiinfectives (antibiotics, antiseptics), n (%)				
Prior to treatment	19 (14)	37 (15)	7 (5)	27 (11)
During treatment	20 (15)	25 (10)	19 (15)	21 (8)
Xanthine, n (%)				

Prior to treatment	10 (8)	21 (8)	8 (6)	23 (9)
During treatment	14 (11)	19 (8)	10 (8)	20 (8)
Mucolytics, n (%)				
Prior to treatment	9 (7)	23 (9)	7 (5)	19 (8)
During treatment	16 (12)	24 (10)	15 (12)	18 (7)

ICS, inhaled corticosteroids; SC, subcutaneous; SCS, systemic corticosteroids.

Table S4. Baseline demographics and clinical characteristics by baseline ICS dose

	SWIFT-1				SWIFT-2			
	Medium-dose ICS*		High-dose ICS*		Medium-dose ICS*		High-dose ICS*	
	Placebo (N=61)	Depemokimab 100 mg SC	Placebo (N=71)	Depemokimab 100 mg SC	Placebo (N=60)	Depemokimab 100 mg SC	Placebo (N=68)	Depemokimab 100 mg SC
Age group (years), n (%)								
12–17	5 (8)	3 (3)	0 (0)	0 (0)	7 (12)	6 (6)	3 (4)	6 (4)
18–64	43 (70)	84 (71)	48 (68)	101 (77)	39 (65)	60 (64)	54 (79)	109 (69)
≥65	13 (21)	31 (26)	23 (32)	31 (23)	14 (23)	28 (30)	11 (16)	43 (27)
Age (years), mean (SD)	50.1 (16.5)	53.6 (14.4)	56.6	54.5 (13.3)	51.8 (17.8)	53.0 (18.4)	50.6 (15.6)	53.9 (14.5)
Female sex, n (%)	38 (62)	73 (62)	41 (58)	71 (54)	39 (65)	65 (69)	42 (62)	95 (60)
Race, n (%)								
White	43 (70)	84 (71)	66 (93)	123 (93)	46 (77)	75 (80)	45 (66)	106 (67)
Other†	18 (30)	34 (29)	5 (7)	9 (7)	14 (23)	19 (20)	23 (34)	52 (33)
Duration of asthma (years), mean	18.2 (17.0)	21.6 (16.7)	21.6	23.3 (15.6)	24.8 (18.4)	28.2 (18.7)	23.5 (17.6)	24.1 (18.6)
Maintenance OCS at baseline, n (%)	7 (11)	2 (2)	6 (8)	6 (5)	1 (2)	4 (4)	5 (7)	9 (6)
Baseline OCS daily dose (mg)‡, mean (SD)	7.1 (3.9)	7.5 (3.5)	10.0 (6.3)	6.7 (2.6)	10.0 (NE)	8.1 (2.4)	6.0 (2.9)	4.7 (2.4)

Peripheral blood eosinophil count, n (%)								
≥150 cells/µl at screening	57 (93)	106 (90)	66 (93)	118 (89)	54 (90)	75 (80)	64 (94)	144 (91)
≥300 cells/µl in 12 months prior to screening	29 (48)	66 (56)	32 (45)	61 (46)	29 (48)	54 (57)	37 (54)	97 (61)
Total IgE (U/mL), geometric mean (SD logs)	n=59[§] 163.9 (1.5)	n=118[§] 142.0 (1.6)	n=71[§] 195.4	n=132[§] 146.6 (1.4)	n=60[§] 143.6 (1.4)	n=91[§] 125.1 (1.5)	n=68[§] 241.4 (1.4)	n=155[§] 181.7 (1.4)
Number of exacerbations requiring OCS/SCS in past 12 months, n (%)								
0	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2	57 (93)	100 (85)	61 (86)	110 (83)	48 (80)	78 (83)	42 (62)	110 (70)
3	4 (7)	15 (13)	5 (7)	17 (13)	9 (15)	12 (13)	8 (12)	24 (15)
4	0 (0)	1 (<1)	3 (4)	1 (<1)	1 (2)	2 (2)	6 (9)	12 (8)
>4	0 (0)	2 (2)	2 (3)	3 (2)	2 (3)	2 (2)	12 (18)	12 (8)

Number of exacerbations requiring hospitalization in past 12 months, n (%)								
0	56 (92)	110 (93)	69 (97)	123 (93)	52 (87)	88 (94)	59 (87)	145 (92)
1	3 (5)	5 (4)	1 (1)	8 (6)	7 (12)	4 (4)	5 (7)	2 (1)
2	2 (3)	3 (3)	1 (1)	1 (<1)	1 (2)	0 (0)	1 (1)	10 (6)
≥3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)	3 (4)	1 (<1)

*Definitions based on GINA 2021 guidelines.

[†]Includes American Indian or Alaska Native, Asian, Black or African American, mixed race, and Native Hawaiian or Other Pacific Islander.

[‡]Prednisone equivalent.

[§]Number of patients with analyzable data at baseline.

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; IgE, immunoglobulin E; OCS, oral corticosteroids; NE, not estimable; SC, subcutaneous; SCS, systemic corticosteroids; SD, standard deviation.

Table S5. Representativeness of trial population

Disease, problem, or condition under investigation	Asthma
Special considerations related to:	
Sex and gender	Asthma is more prevalent and severe in males versus females prior to puberty, but becomes more common in females post-puberty.[14] Behaviours linked to or associated with gender may influence asthma risk, control and outcomes in both men and women.[15]
Age	Asthma prevalence is highest globally in children aged 5–9 years and peaks at 7.5 years.[16]
Race or ethnic group	There are significant differences in asthma burden based on race or ethnic group. These differences may vary between countries. In a meta-analysis from the United Kingdom, patients who are members of ethnic minority groups show higher levels of uncontrolled disease compared with White patients.[17] In the US, asthma is more prevalent among Puerto Rican and non-

	Hispanic Black children than among non-Hispanic White and Mexican American children. Also, asthma mortality rates are twice as high for African Americans in the US as for White Americans.[18]
Geography	Asthma is widespread globally,[19] but is most prevalent in South Asia, high-income North America and Western Europe (as of 2019).[16]
Other considerations	Not applicable
Overall representativeness of this trial	The patients in the present trials demonstrated the expected ratio of females to males (approximately 60:40). Biological sex was reported by patients; they were asked by investigators, "What is your sex?"; the options were female or male. Gender was not reported. Approximately 70% of patients in these trials were aged 18–64 years; 25% were aged over 65 years, and 4% were adolescents. Taking into account national policies (i.e. lack of permission to include patients aged <18 years in various countries), these data are representative of the general population. Patients were recruited from Europe, North America, Asia and Australia. Approximately 12% of patients were Hispanic or Latino, which is representative of the countries included in the studies. The majority of patients were White (77%); 17% were Asian and 5% were Black or African American. Again, this is considered representative of the included countries.

Table S6. SGRQ total score and ACQ-5 score responder status at Week 52

	SWIFT-1		SWIFT-2		Pooled	
	Placebo (N=132)	**Depemokimab 100 mg SC (N=250)**	**Placebo (N=128)**	**Depemokimab 100 mg SC (N=252)**	**Placebo (N=260)**	**Depemokimab 100 mg SC (N=502)**
SGRQ responder status at Week 52, n/n* (%)	74/129 (57)	151/241 (63)	81/125 (65)	164/247 (66)	155/254 (61)	315/488 (65)
Odds ratio (95% CI)	1.27 (0.80, 2.02)		1.07 (0.67, 1.71)		1.11 (0.80, 1.53)	
ACQ-5 responder status at Week 52, n/n* (%)	71/129 (55)	131/241 (54)	66/125 (53)	134/247 (54)	137/254 (54)	265/488 (54)
Odds ratio (95% CI)	0.95 (0.60, 1.52)		1.06 (0.67, 1.69)		1.00 (0.72, 1.38)	

SGRQ score range is 0–100; higher scores indicate worse quality of life; within-patient MCID: -4.0.[9] ACQ-5 score range is 0–6; higher scores indicate worse asthma control; within-patient MCID: -0.5.[10] Responses defined as meeting the within-patient MCID. CI widths have not been adjusted for multiplicity and should not be used for inferential purposes.

*Number of patients with analyzable data at Week 52.

ACQ-5, Asthma Control Questionnaire-5; CI, confidence interval; MCID, minimal clinically important difference; SC, subcutaneous; SGRQ, St George's Respiratory Questionnaire.

Table S7. Time to first exacerbation requiring hospitalization and/or ER visit

	SWIFT-1		SWIFT-2	
	Placebo (N=132)	**Depemokimab 100 mg SC (N=250)**	**Placebo (N=128)**	**Depemokimab 100 mg SC (N=252)**
Patients with event, n (%)	11 (8)	3 (1)	13 (10)	10 (4)
Patients without an event (censored), n (%)	121 (92)	247 (99)	115 (90)	242 (96)
Hazard ratio (depemokimab-placebo) (95% CI)	NA*		0.36 (0.15, 0.82)	

*In line with the statistical analysis plan, exacerbations requiring hospitalization and/or ER visit were not analyzed in SWIFT-1 as fewer than 20 occurred in the study.

Hazard ratio and 95% CI are from a Cox proportional hazards model with covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, ≥4), geographical region and baseline pre-bronchodilator percent predicted FEV_1.

CI, confidence interval; ER, emergency room; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroids; SC, subcutaneous.

Table S8. Change from baseline in PROMIS fatigue item score at Week 52

	SWIFT-1		SWIFT-2	
	Placebo (N=65)	**Depemokimab 100 mg SC (N=122)**	**Placebo (N=66)**	**Depemokimab 100 mg SC (N=128)**
n				
Baseline	63	115	65	124
Change from baseline at Week 52	51	98	57	108
Energy to exercise strenuously, mean (SD)				
Baseline	3.6 (1.15)	3.7 (1.12)	3.6 (1.14)	3.7 (1.22)
Change from baseline at Week 52	-0.4 (1.52)	-0.6 (1.31)	-0.6 (1.54)	-0.4 (1.42)
Enough energy to enjoy things, mean (SD)				
		3.0 (1.00)		

Baseline	2.9 (1.08)	-0.6 (1.19)	2.7 (0.91)	2.7 (1.10)
Change from baseline at Week 52	-0.5 (0.99)		-0.5 (1.56)	-0.2 (1.61)
Run out of energy, mean (SD)				
Baseline	3.0 (0.92)	3.1 (0.97)	2.9 (0.91)	2.9 (1.10)
Change from baseline at Week 52	-0.4 (0.94)	-0.6 (0.99)	-0.6 (1.03)	-0.6 (1.08)

Scale: 1–5 per item. Higher scores indicate worse fatigue. No MCID available.

PROMIS, Patient-Reported Outcomes Measurement Information System; MCID, minimal clinically important difference; SC, subcutaneous; SD, standard deviation.

Table S9. Change from baseline in SNOT-22 score at Week 52

	SWIFT-1		SWIFT-2	
	Placebo (N=132)	**Depemokimab 100 mg SC (N=250)**	**Placebo (N=128)**	**Depemokimab 100 mg SC (N=252)**
Baseline, mean (SD)	n=129 30.4 (19.49)	n=241 29.7 (19.17)	n=125 28.2 (18.63)	n=247 29.3 (19.11)
Change from baseline at Week 52, mean (SD)	n=114 -3.6 (16.26)	n=220 -6.3 (18.10)	n=116 -7.5 (15.05)	n=221 -8.3 (17.08)

Scale: 0–110. Higher scores indicate worse quality of life. Within-patient MCID: -8.9.[20]

MCID, minimal clinically important difference; SC, subcutaneous; SD, standard deviation; SNOT-22, 22-Item SinoNasal Outcomes Test.

Table S10. Patient-rated response to therapy at Week 52

	SWIFT-1		SWIFT-2	
	Placebo (N=132)	**Depemokimab 100 mg SC (N=250)**	**Placebo (N=128)**	**Depemokimab 100 mg SC (N=252)**
n	117	227	116	225
Significantly improved, n (%)	19 (16)	64 (28)	27 (23)	58 (26)
Moderately improved, n (%)	25 (21)	48 (21)	20 (17)	45 (20)
Mildly improved, n (%)	23 (20)	32 (14)	27 (23)	47 (21)
No change, n (%)	46 (39)	70 (31)	38 (33)	66 (29)
Mildly worse, n (%)	4 (3)	8 (4)	3 (3)	6 (3)

Moderately worse, n (%)	0 (0)	4 (2)	1 (<1)	1 (<1)
Significantly worse, n (%)	0 (0)	1 (<1)	0 (0)	2 (<1)

SC, subcutaneous.

Table S11. Clinician-rated response to therapy at Week 52

	SWIFT-1		SWIFT-2	
	Placebo (N=132)	**Depemokimab 100 mg SC (N=250)**	**Placebo (N=128)**	**Depemokimab 100 mg SC (N=252)**
n	122	235	119	233
Significantly improved, n (%)	19 (16)	39 (17)	18 (15)	60 (26)
Moderately improved, n (%)	30 (25)	75 (32)	35 (29)	75 (32)
Mildly improved, n (%)	43 (35)	71 (30)	26 (22)	52 (22)
No change, n (%)	26 (21)	43 (18)	38 (32)	43 (18)
Mildly worse, n (%)	2 (2)	6 (3)	1 (<1)	3 (1)

Moderately worse, n (%)	2 (2)	1 (<1)	1 (<1)	0 (0)
Significantly worse, n (%)	0 (0)	0 (0)	0 (0)	0 (0)

SC, subcutaneous.

Table S12. PGI-S at baseline and Week 52

	SWIFT-1		SWIFT-2	
	Placebo (N=132)	**Depemokimab 100 mg SC (N=250)**	**Placebo (N=128)**	**Depemokimab 100 mg SC (N=252)**
Baseline	n=128	n=241	n=125	n=246
No symptoms	7 (5)	11 (5)	11 (9)	19 (8)
Mild	41 (32)	89 (37)	49 (39)	80 (33)
Moderate	65 (51)	106 (44)	50 (40)	117 (48)
Severe	12 (9)	32 (13)	14 (11)	25 (10)
Very severe	3 (2)	3 (1)	1 (<1)	5 (2)
Week 52	n=117	n=227	n=117	n=225
No symptoms	15 (13)	53 (23)	22 (19)	60 (27)
Mild	58 (50)	94 (41)	60 (51)	96 (43)

Moderate	39 (33)	65 (29)	30 (26)	55 (24)
Severe	2 (2)	14 (6)	5 (4)	13 (6)
Very severe	3 (3)	1 (<1)	0 (0)	1 (<1)

PGI-S, Patient Global Impression of Asthma Severity; SC, subcutaneous.

Table S13. PGI-C from baseline of asthma severity at Week 52

	SWIFT-1		SWIFT-2	
	Placebo (N=132)	**Depemokimab 100 mg SC (N=250)**	**Placebo (N=128)**	**Depemokimab 100 mg SC (N=252)**
n	117	227	n=116	n=225
Much better, n (%)	37 (32)	102 (45)	45 (39)	113 (50)
A little better, n (%)	43 (37)	69 (30)	40 (34)	72 (32)
No change, n (%)	33 (28)	46 (20)	29 (25)	34 (15)
A little worse, n (%)	2 (2)	8 (4)	2 (2)	4 (2)
Much worse, n (%)	2 (2)	2 (<1)	0 (0)	2 (<1)

PGI-C, Patient Global Impression of Asthma Change; SC, subcutaneous.

Table S14. ANSD/ADSD weekly mean score responder status at Week 52

	SWIFT-1		SWIFT-2	
	Placebo (N=112)	**Depemokimab 100 mg SC (N=212)**	**Placebo (N=128)**	**Depemokimab 100 mg SC (N=252)**
ANSD	n=102	n=192	n=120	n=238
Responder, n (%)	18 (18)	36 (19)	16 (13)	45 (19)
Non-responder, n (%)	84 (82)	156 (81)	104 (87)	193 (81)
Odds ratio (depemokimab-placebo) (95% CI)	1.12 (0.60, 2.10)		1.59 (0.83, 3.06)	
ADSD	n=112	n=211	n=127	n=250
Responder, n (%)	32 (29)	57 (27)	23 (18)	58 (23)
Non-responder, n (%)	80 (71)	154 (73)	104 (82)	192 (77)

Odds ratio (depemokimab-placebo) (95% CI)	0.95 (0.56, 1.63)	1.45 (0.81, 2.61)

ADSD/ANSD score range is 0–10; higher scores indicate worse symptoms; within-patient MCID: -1.5 for ANSD and -1.2 for ADSD.[11] Responses defined as meeting the within-patient MCID. CI widths have not been adjusted for multiplicity and should not be used for inferential purposes.

ADSD/ANSD, asthma daily/nightly symptom diary; CI, confidence interval; SC, subcutaneous; SD, standard deviation**.**

Table S15. Change from baseline in 2-week mean number of occasions of rescue medication (salbutamol/albuterol) per day at Week 51–52

	SWIFT-1		SWIFT-2	
	Placebo (N=132)	**Depemokimab 100 mg SC (N=250)**	**Placebo (N=128)**	**Depemokimab 100 mg SC (N=252)**
Baseline, mean (SD)	n=132 1.26 (1.773)	n=248 1.31 (1.728)	n=127 1.17 (1.537)	n=249 1.25 (1.596)
Change from baseline at Week 51–52, mean (SD)	n=86 -0.32 (1.622)	n=166 -0.36 (1.706)	n=79 -0.38 (1.647)	n=157 -0.57 (1.129)

SC, subcutaneous; SD, standard deviation.

Table S16. Change from baseline in 2-week mean number of awakenings at night due to asthma symptoms requiring rescue medication use per night at Week 51–52

	SWIFT-1		SWIFT-2	
	Placebo (N=132)	**Depemokimab 100 mg SC (N=250)**	**Placebo (N=128)**	**Depemokimab 100 mg SC (N=252)**
Baseline, mean (SD)	n=132 0.70 (0.960)	n=249 0.71 (0.951)	n=127 0.56 (0.806)	n=246 0.66 (0.978)
Change from baseline at Week 51–52, mean (SD)	n=86 -0.37 (1.072)	n=166 -0.48 (0.896)	n=79 -0.25 (0.651)	n=156 -0.38 (0.681)

SC, subcutaneous; SD, standard deviation.

Table S17. Change from baseline in 2-week mean morning PEF (L/min) at Week 51–52

	SWIFT-1		SWIFT-2	
	Placebo (N=132)	**Depemokimab 100 mg SC (N=250)**	**Placebo (N=128)**	**Depemokimab 100 mg SC (N=252)**
Baseline, mean (SD)	n=132 270.45 (120.256)	n=248 287.43 (119.739)	n=126 291.11 (101.239)	n=247 292.85 (111.298)
Change from baseline at Week 51–52, mean (SD)	n=85 14.37 (61.841)	n=162 15.20 (58.657)	n=76 4.36 (55.794)	n=150 33.84 (69.652)

PEF, peak expiratory flow; SC, subcutaneous; SD, standard deviation.

Table S18. Change from baseline in weekly mean daily asthma symptom scores at Week 51–52

	SWIFT-1		SWIFT-2	
	Placebo (N=132)	**Depemokimab 100 mg SC (N=250)**	**Placebo (N=128)**	**Depemokimab 100 mg SC (N=252)**
Baseline, mean (SD)	n=132 1.75 (1.164)	n=248 1.77 (1.183)	n=127 1.65 (1.182)	n=249 1.75 (1.202)
Change from baseline at Week 51–52, mean (SD)	n=86 -0.36 (1.162)	n=166 -0.65 (1.076)	n=79 -0.62 (0.942)	n=157 -0.72 (1.158)

Scale: 0–5; 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.

SC, subcutaneous; SD, standard deviation.

Table S19. Number of days with OCS over 52 weeks

	SWIFT-1		SWIFT-2	
	Placebo (N=132)	**Depemokimab 100 mg SC (N=250)**	**Placebo (N=128)**	**Depemokimab 100 mg SC (N=252)**
Total number of days with OCS associated with exacerbation in patients who report an exacerbation requiring OCS per patient, mean (SD)	n=58 23.1 (25.37)	n=75 13.1 (9.72)	n=61 19.5 (20.31)	n=81 16.9 (25.48)

OCS, oral corticosteroids; SC, subcutaneous; SD, standard deviation.

Table S20. Annualized rate of exacerbations in the pre-specified China subpopulation of SWIFT-1*

	Placebo (n=20)	Depemokimab 100 mg SC (n=38)
Annualized rate of exacerbations over 52 weeks (95% CI)	2.08 (1.35, 3.21)	0.32 (0.18, 0.58)
Rate ratio (95% CI)	0.15 (0.07, 0.33)	
Percentage reduction in annual rate (95% CI)	85 (67, 93)	
Number of exacerbations	41	13

*SWIFT-2 did not enroll patients from China.

CI widths have not been adjusted for multiplicity and should not be used for inferential purposes.

CI, confidence interval; SC, subcutaneous.

Table S21. On-treatment AEs by system organ class and preferred term (≥5 patients across both arms in either trial)

	SWIFT-1		SWIFT-2	
System organ class Preferred term	**Placebo (N=132)**	**Depemokimab 100 mg SC (N=250)**	**Placebo (N=129*)**	**Depemokimab 100 mg SC (N=251)**
Infections and infestations, n (%)	77 (58)	146 (58)	76 (59)	134 (53)
COVID-19	29 (22)	51 (20)	19 (15)	37 (15)
Nasopharyngitis	25 (19)	29 (12)	27 (21)	33 (13)
Upper respiratory tract infection	14 (11)	25 (10)	6 (5)	21 (8)
Rhinitis	10 (8)	15 (6)	5 (4)	7 (3)
Influenza	2 (2)	19 (8)	9 (7)	5 (2)
Bronchitis	5 (4)	12 (5)	10 (8)	12 (5)
Sinusitis	6 (5)	11 (4)	6 (5)	11 (4)
Lower respiratory tract infection	5 (4)	10 (4)	5 (4)	4 (2)

Respiratory tract infection	6 (5)	8 (3)	4 (3)	5 (2)
Laryngitis	4 (3)	9 (4)	2 (2)	2 (<1)
Pharyngitis	2 (2)	8 (3)	1 (<1)	10 (4)
Pneumonia	4 (3)	5 (2)	3 (2)	3 (1)
Acute sinusitis	1 (<1)	6 (2)	3 (2)	6 (2)
Urinary tract infection	1 (<1)	4 (2)	4 (3)	6 (2)
Conjunctivitis	1 (<1)	3 (1)	2 (2)	3 (1)
Respiratory, thoracic and mediastinal disorders, n (%)	22 (17)	39 (16)	22 (17)	46 (18)
Cough	6 (5)	9 (4)	3 (2)	6 (2)
Allergic rhinitis	4 (3)	11 (4)	3 (2)	18 (7)
Asthma	6 (5)	4 (2)	9 (7)	8 (3)
Dyspnoea	3 (2)	5 (2)	1 (<1)	7 (3)
Oropharyngeal pain	0 (0)	4 (2)	5 (4)	3 (1)
Musculoskeletal and connective tissue disorders, n (%)	20 (15)	28 (11)	22 (17)	38 (15)

Back pain	7 (5)	6 (2)	6 (5)	7 (3)
Arthralgia	3 (2)	5 (2)	5 (4)	14 (6)
Myalgia	2 (2)	3 (1)	2 (2)	2 (<1)
Pain in extremity	0 (0)	5 (2)	1 (<1)	4 (2)
Neck pain	1 (<1)	0 (0)	3 (2)	2 (<1)
Osteoarthritis	0 (0)	2 (<1)	1 (<1)	4 (2)
Gastrointestinal disorders, n (%)	15 (11)	30 (12)	16 (12)	34 (14)
Gastrooesophageal reflux disease	4 (3)	2 (<1)	1 (<1)	3 (1)
Upper abdominal pain	2 (2)	4 (2)	1 (<1)	3 (1)
Abdominal pain	2 (2)	3 (1)	0 (0)	4 (2)
Diarrhoea	1 (<1)	4 (2)	3 (2)	8 (3)
Vomiting	1 (<1)	1 (<1)	3 (2)	3 (1)
Nausea	0 (0)	3 (1)	4 (3)	1 (<1)
Nervous system disorders, n (%)	17 (13)	27 (11)	14 (11)	36 (14)

Headache	10 (8)	12 (5)	10 (8)	20 (8)
Dizziness	1 (<1)	2 (<1)	1 (<1)	8 (3)
Skin and subcutaneous tissue disorders, n (%)	12 (9)	17 (7)	5 (4)	18 (7)
Rash	3 (2)	2 (<1)	0 (0)	0 (0)
Urticaria	0 (0)	1 (<1)	1 (<1)	5 (2)
Pruritus	2 (2)	0 (0)	0 (0)	5 (2)
Injury, poisoning and procedural complications, n (%)	11 (8)	15 (6)	10 (8)	27 (11)
General disorders and administration site conditions, n (%)	7 (5)	17 (7)	15 (12)	22 (9)
Pyrexia	1 (<1)	4 (2)	3 (2)	7 (3)
Influenza-like illness	0 (0)	4 (2)	1 (<1)	5 (2)
Fatigue	0 (0)	0 (0)	2 (2)	4 (2)
Asthenia	0 (0)	0 (0)	2 (2)	3 (1)
Chest pain	0 (0)	4 (2)	2 (2)	3 (1)

Vascular disorders, n (%)	8 (6)	13 (5)	9 (7)	9 (4)
Hypertension	7 (5)	9 (4)	7 (5)	6 (2)
Investigations, n (%)	8 (6)	12 (5)	5 (4)	9 (4)
Alanine aminotransferase increased	2 (2)	3 (1)	0 (0)	3 (1)
Cardiac disorders, n (%)	5 (4)	10 (4)	4 (3)	4 (2)
Metabolism and nutrition disorders, n (%)	7 (5)	7 (3)	9 (7)	12 (5)
Diabetes mellitus	2 (2)	0 (0)	2 (2)	3 (1)
Eye disorders, n (%)	2 (2)	9 (4)	4 (3)	13 (5)
Allergic conjunctivitis	2 (2)	5 (2)	2 (2)	6 (2)
Reproductive system and breast disorders, n (%)	7 (5)	3 (1)	3 (2)	3 (1)
Hepatobiliary disorders, n (%)	5 (4)	5 (2)	1 (<1)	3 (1)

Neoplasms benign, malignant and unspecified (incl. cysts and polyps), n (%)	5 (4)	4 (2)	1 (<1)	4 (2)
Blood and lymphatic system disorders, n (%)	3 (2)	5 (2)	2 (2)	5 (2)
Anaemia	2 (2)	4 (2)	1 (<1)	3 (1)
Ear and labyrinth disorders, n (%)	1 (<1)	6 (2)	3 (2)	5 (2)
Psychiatric disorders, n (%)	2 (2)	5 (2)	2 (2)	7 (3)
Immune system disorders, n (%)	2 (2)	4 (2)	4 (3)	5 (2)
Renal and urinary disorders, n (%)	1 (<1)	3 (1)	3 (2)	2 (<1)

*****One patient randomized to the depemokimab group received placebo and was therefore included in the placebo group for safety analyses in line with the predefined analysis sets.

AE, adverse event; SC, subcutaneous.

Table S22. On- and post-treatment AESI – incidence, relative risk and risk difference

	SWIFT-1				SWIFT-2			
	Placebo (N=132)	**Depemokimab 100 mg SC (N=250)**	**Relative risk (95% CI)**	**% risk difference (Exact 95% CI)**	**Placebo (N=129*)**	**Depemokimab 100 mg SC (N=251)**	**Relative risk (95% CI)**	**% risk difference (Exact 95% CI)**
Allergic (type I hypersensitivity), n (%)	0 (0)	0 (0)	NE	0 (NA)	0 (0)	0 (0)	NE	0 (NA)
Anaphylaxis, n (%)	0 (0)	0 (0)	NE	0 (NA)	0 (0)	0 (0)	NE	0 (NA)
Other systemic reactions, n (%)	2 (2)	2 (<1)	0.53 (0.08, 3.71)	-0.7 (-4.7, 1.7)	0 (0)	6 (2)	NE	2.4 (-0.7, 5.2)

Type III hypersensitivity/ vasculitis, n (%)	0 (0)	0 (0)	NE	0 (NA)	0 (0)	0 (0)	NE	0 (NA)
Local injection site reactions, n (%)	1 (<1)	3 (1)	1.58 (0.17, 15.08)	0.4 (-3.1, 2.9)	1 (<1)	4 (2)	2.06 (0.23, 18.20)	0.8 (-2.9, 3.5)

*****One patient randomized to the depemokimab group received placebo and was therefore included in the placebo group for safety analyses in line with the predefined analysis sets.

A relative risk of 1 = no difference in risk between treatments, <1 favors depemokimab, and >1 favors placebo. A risk difference of 0 = no difference in risk between treatments, <0 favors depemokimab, and >0 favors placebo.

AESI, adverse event of special interest; CI, confidence interval; NA, not applicable; NE, not estimable; SC, subcutaneous.

Table S23. Change from baseline in incidence of binding anti-drug antibodies

Planned timepoint	Assay result	SWIFT-1		SWIFT-2	
		Placebo (N=132)	Depemokimab 100 mg SC (N=250)	Placebo (N=129)	Depemokimab 100 mg SC (N=251)
Baseline	n	132	246	128	249
	Negative, n (%)	132 (100)	245 (>99)	128 (100)	249 (100)
	Positive, n (%)	0 (0)	1 (<1)	0 (0)	0 (0)
	Titer value*				
	Min.	NE	80	NE	NE
	Median	NE	80	NE	NE
	Max.	NE	80	NE	NE

Week 52	n	-	230	-	230
	Negative		221 (96)		227 (99)
	Positive		9 (4)		3 (1)
	Transient positive		0 (0)		0 (0)
	Persistent positive		9 (4)		3 (1)
	Titer value*				
	Min.		80		80
	Median		80		160
	Max.		160		320
Worst case post-baseline	n	-	249	-	250
	Negative		218 (88)		237 (95)
	Positive		31 (12)		13 (5)

	Transient positive		8 (3)		7 (3)
	Persistent positive		23 (9)		6 (2)
	Titer value*				
	Min.		80		80
	Median		80		80
	Max.		160		320

*Titer is only measured when a positive result is found.

NE, not estimable; SC, subcutaneous.

Table S24. Sensitivity analysis of annualized rate of clinically significant exacerbations (tipping point analysis)

Multiplicative delta for depemokimab rate imputation	Multiplicative delta for placebo rate imputation											
	SWIFT-1						SWIFT-2					
	0.0625	0.2500	1.0000	4.0000	16.0000	64.0000	0.0625	0.2500	1.0000	4.0000	16.0000	64.0000
0.0625	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
0.2500	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
1.0000	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
4.0000	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.002*	0.002*	0.002*	<0.001*	<0.001*	<0.001*
16.0000	0.002*	0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.176	0.170	0.147	0.101	0.032*	0.004*
64.0000	0.345	0.332	0.257	0.124	0.015*	<0.001*	0.350	0.356	0.398	0.480	0.768	0.583

Analysis performed using a generalised linear model assuming a negative binomial distribution and covariates of treatment group, baseline ICS dose (medium or high), exacerbation history (2, 3, ≥4), geographical region and baseline pre-bronchodilator percent predicted FEV_1. Delta is the multiplier

applied to the MAR-estimated rate of exacerbations per year following study withdrawal; delta values <1 represent exacerbation rates less than the MAR-estimated rate, delta values =1 represent the MAR-estimated rate of exacerbations, and delta values >1 represent exacerbation rates that are higher than the MAR-estimated rate..

*p-values which are significant in favor of depemokimab at the 5% significance level.

FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroids; MAR, missing at random.

Supplementary Appendix References

1. Singh DA-O, Fuhr R, Bird NA-O, et al. A Phase 1 study of the long-acting anti-IL-5 monoclonal antibody GSK3511294 in patients with asthma. British Journal of Clinical Pharmacology 2022;88(2):702-712. (In eng).
2. Ortega Hector G, Liu Mark C, Pavord Ian D, et al. Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma. New England Journal of Medicine 2014;371(13):1198-1207. DOI: 10.1056/NEJMoa1403290.
3. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. The Lancet Respiratory Medicine 2017;5(5):390-400. DOI: 10.1016/S2213-2600(17)30125-X.
4. National Institutes of Health. National Heart, Lung, and Blood Institute (NHLBI). Guidelines for the Diagnosis and Management of Asthma (EPR-3). Aug 2007. Retrieved 19 July, 2024, from https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-ofasthma
5. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention (2020). Retrieved 21 July, 2024, from https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf.
6. PASS. Sample Size Software: Tests for the Ratio of Two Negative Binomial Rates. Retrieved 22 July, 2024, from https://www.ncss.com/wp-content/themes/ncss/pdf/Procedures/PASS/Tests_for_the_Ratio_of_Two_Negative_Binomial_Rates.pdf.
7. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. The Lancet 2012;380:651-59.

8. Keene ON, Roger JH, Hartley BF, Kenward MG. Missing data sensitivity analysis for recurrent event data using controlled imputation. Pharmaceutical Statistics 2014;13:258-64.
9. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. European Respiratory Journal 2002;19:398-404.
10. Juniper EF, Svensson K, Mork A-C, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respiratory Medicine 2005;99:553-558.
11. Keeley T, Cristancho RA, Dumi G, Turner R, O'Neill D. Measuring Meaningful Change in Patients With Asthma Using the Asthma Daytime and Asthma Nighttime Symptom Diaries. Am J Respir Crit Care Med 2024;209:A1390.
12. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. The Lancet 2016;388:2128-41.
13. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. New England Journal of Medicine 2021;384:1800-9.
14. Fuseini H, Newcomb DC. Mechanisms Driving Gender Differences in Asthma. Curr Allergy Asthma Rep 2017;17:19.
15. Jenkins CR, et al. Personalized Treatment of Asthma: The Importance of Sex and Gender Differences. *J Allergy Clin Immunol Pract* 2022;10:963-71.
16. Wang Z, et al. Global, regional, and national burden of asthma and its attributable risk factors from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. Respiratory Research 2023;24:169.

17. Busby J et al. The impact of ethnicity on disease presentation and control in severe asthma. European Respiratory Journal 2021;58:Suppl.65:OA1325.
18. Perez MF and MT Coutinho. An Overview of Health Disparities in Asthma. *Yale J Biol Med* 2021;94(3):497–507.
19. Global Asthma Network. Global Asthma Report 2022. Retrieved 22 July, 2024, from https://globalasthmareport.org/resources/Global_Asthma_Report_2022.pdf.
20. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clinical Otolaryngology* 2009;34(5):447-54.