ORIGINAL ARTICLE

Twice-Yearly Depemokimab in Severe Asthma with an Eosinophilic Phenotype

David J. Jackson, Ph.D., Michael E. Wechsler, M.D., Daniel J. Jackson, M.D., David Bernstein, M.D., Stephanie Korn, M.D., Ph.D., Paul E. Pfeffer, Ph.D., Ruchong Chen, M.D., Ph.D., Junpei Saito, M.D., Ph.D., Gustavo de Luíz Martinez, M.D., Lucyna Dymek, M.D., Ph.D., Loretta Jacques, Ph.D., Nicholas Bird, M.Sc., Stein Schalkwijk, Pharm.D., Ph.D., Douglas Smith, M.B.A., Peter Howarth, D.M., and Ian D. Pavord, D.M., F.Med.Sci., for the SWIFT-1 and SWIFT-2 Investigators*

ABSTRACT

BACKGROUND

Depemokimab is an ultra-long-acting biologic therapy with enhanced binding affinity for interleukin-5 that may enable effective 6-month dosing intervals.

METHODS

In these phase 3A, randomized, placebo-controlled replicate trials, we evaluated the efficacy and safety of depemokimab in patients with severe asthma and an eosinophilic phenotype characterized by a high eosinophil count (≥300 cells per microliter in the previous 12 months or ≥150 cells per microliter at screening) and a history of exacerbations despite the receipt of medium- or high-dose inhaled glucocorticoids. Patients were randomly assigned in a 2:1 ratio to receive either depemokimab (at a dose of 100 mg subcutaneously) or placebo at weeks 0 and 26, plus standard care. The primary end point was the annualized rate of exacerbations at 52 weeks. Secondary end points, which were analyzed in a hierarchical manner to adjust for multiplicity, included the change from baseline in the score on the St. George's Respiratory Questionnaire (SGRQ), the forced expiratory volume in 1 second, and asthma symptom reports at 52 weeks.

RESULTS

Across the two trials, 792 patients underwent randomization and 762 were included in the full analysis; 502 were assigned to receive depemokimab and 260 to receive placebo. The annualized rate of exacerbations was 0.46 (95% confidence interval [CI]), 0.36 to 0.58) with depemokimab and 1.11 (95% CI, 0.86 to 1.43) with placebo (rate ratio, 0.42; 95% CI, 0.30 to 0.59; P<0.001) in SWIFT-1 and 0.56 (95% CI, 0.44 to 0.70) with depemokimab and 1.08 (95% CI, 0.83 to 1.41) with placebo (rate ratio, 0.52; 95% CI, 0.36 to 0.73; P<0.001) in SWIFT-2. No significant between-group difference in the change from baseline in the SGRQ score was observed in either trial, so no statistical inference was drawn on subsequent secondary end points. The proportion of patients with any adverse event was similar in the two groups in both trials.

CONCLUSIONS

Depemokimab reduced the annualized rate of exacerbations among patients with severe asthma with an eosinophilic phenotype. (Funded by GSK; SWIFT-1 and SWIFT-2 ClinicalTrials.gov numbers, NCT04719832 and NCT04718103.)

The authors' affiliations are listed in the Appendix. Dr. Pavord can be contacted at ian.pavord@ndm.ox.ac.uk or at the Respiratory Medicine Unit and NIHR Oxford Biomedical Research Centre, Nuffield Department of Medicine, University of Oxford, Rm. 7400, Level 7EF, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, United Kingdom.

*The SWIFT-1 and SWIFT-2 investigators are listed in the Supplementary Appendix, available at NEJM.org.

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Inadequately controlled asthma can result in episodic severe exacerbations despite treatment with medium- or high-dose inhaled glucocorticoids plus additional controller medications.[1,2] Patients with frequent asthma exacerbations often have a high level of unregulated type 2 inflammation, which generates the classic T2 cytokines, interleukin-4, interleukin-5, and interleukin-13.[3,4] Interleukin-5 is responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils,[5] as well as for influencing the activity of a range of other inflammatory and structural airway cells.[6-8] Uncontrolled eosinophilic inflammation, which is reflective of disease driven by interleukin-5, is a recognized risk factor for severe disease exacerbations, airway remodeling, and decline in lung function among patients with asthma.[5,9] The majority of patients with severe asthma have a blood eosinophil count of at least 150 cells per microliter.[10]

In 2009, proof-of-concept trials showed that the anti–interleukin-5 antibody mepolizumab reduced the frequency of exacerbations in patients who had a sputum eosinophil count of more than 3% and a history of exacerbations.[11] Mepolizumab also led to a reduction in the use of oral glucocorticoids in patients with persistent sputum eosinophilia after treatment with oral glucocorticoids and high-dose inhaled glucocorticoids.[12] In a phase 2 study,[13] investigators identified the blood eosinophil count as a predictive biomarker of the response to mepolizumab. Phase 3 trials confirmed a reduction in exacerbations and in the frequency of oral glucocorticoid use in patients with severe asthma and a blood eosinophil count of at least 150 cells per microliter at screening or at least 300 cells per microliter in the previous year.[13-15] Other biologic therapies that target interleukin-5 or the interleukin-5 receptor have also been shown to improve outcomes in patients with asthma with an eosinophilic phenotype.[16-18]

Depemokimab is an ultra-long-acting biologic therapy with enhanced binding affinity for interleukin-5, which potentially enables effective 6-month dosing intervals for patients with asthma.[19] In a single-dose phase 1 study,[19] researchers found that depemokimab had an acceptable safety profile in adult patients with mild or moderate asthma and a blood eosinophil count of at least 200 cells per microliter at screening and led to dose-dependent suppression of the blood eosinophil count that was sustained over a 26-week period.[19]

We designed the phase 3A SWIFT-1 and SWIFT-2 replicate trials to investigate the efficacy and safety of depemokimab as an adjunctive treatment to standard care for patients who had severe asthma with an eosinophilic phenotype and a history of exacerbations despite the receipt of medium- or high-dose inhaled glucocorticoids.

Methods

Trial Design and Oversight

SWIFT-1 and SWIFT-2 were both multicenter, randomized, double-blind, placebo-controlled trials (Fig. S1A in the Supplementary Appendix, available with the full text of this article at NEJM.org). SWIFT-1 was conducted from March 17, 2021, to November 21, 2023, in 12 countries at 86 sites; SWIFT-2 was conducted from February 4, 2021, to April 11, 2024, in 11 countries at 131 sites. Patients participated in 17 visits (once every 4 weeks, with an extra visit 2 weeks after each dosing) from screening to the end of the trial. The on-treatment period included any events or assessments that occurred between the first dose of depemokimab or placebo and 182 days after the last dose. Additional details regarding the trial design are provided in the Supplementary Appendix.

The two trials were conducted in accordance with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences, applicable International Council for Harmonisation Good Clinical Practice guidelines, and all applicable laws and regulations. The institutional review board or ethics committee at each site approved the trial protocol (available at NEJM.org) and any other relevant documents. Important amendments to the protocol are detailed in the Supplementary Appendix.

The trial funder, GSK, designed and oversaw the trial conduct, along with the collection and analysis of the data. Data were also analyzed by employees of Veramed, a clinical research organization. Details regarding the authors' contributions to the trial design, data collection and analysis, and manuscript development are pro-

vided in the Supplementary Appendix. Medical writers who were funded by GSK prepared the first draft of the manuscript under the authors' direction. The manuscript was reviewed and edited by the authors. The authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PATIENTS

Key eligibility criteria were an age of at least 12 years, an asthma diagnosis by a physician at least 2 years earlier, a blood eosinophil count of at least 300 cells per microliter during the previous 12 months or a count of at least 150 cells per microliter at screening, regular treatment with medium- or high-dose inhaled glucocorticoids in the previous 12 months (as defined according to the 2021 guidelines of the Global Initiative for Asthma[20]), current treatment with at least one additional controller for at least 3 months, and a history of at least two exacerbations resulting in the administration of systemic glucocorticoids in the previous 12 months.

All the patients were required to have airflow obstruction, as determined by measurement of the forced expiratory volume in 1 second (FEV_1) before bronchodilation. Adults (≥18 years of age) were required to have an FEV_1 of less than 80% of the predicted value, according to the criteria of the third National Health and Nutrition Examination Survey (NHANES III), and children between the ages of 12 and 17 years were required to have an FEV_1 of less than 90% of the predicted value or a ratio of the FEV_1 to the forced vital capacity of less than 0.8.

Any score on the Asthma Control Questionnaire–5 was acceptable for enrollment. Patients who were receiving a biologic therapy as part of their current maintenance therapy or who had received an anti–interleukin-5 antibody in the previous 12 months were excluded. Comprehensive eligibility criteria are detailed in the Supplementary Appendix.

TREATMENTS AND RANDOMIZATION

Patients underwent randomization in a 2:1 ratio to receive either depemokimab (at a dose of 100 mg) or placebo subcutaneously at week 0 and week 26, in addition to standard care. Both depemokimab and placebo were administered with a prefilled syringe assembled in a syringe safety device. The randomization schedule was generated with the use of RandAll NG software and was performed by means of interactive-response technology with a block size of six. Separate randomization schedules were created for each country. Randomization was stratified according to the dose of inhaled glucocorticoids (medium or high) that the patient was receiving at baseline. Trial staff members, patients, and investigators were unaware of trial-group assignments.

TRIAL END POINTS AND ASSESSMENTS

The primary end point was the annualized rate of exacerbations during a 52-week period. An asthma exacerbation was defined as a worsening of asthma leading to the use of systemic glucocorticoids (or at least a doubling in the dose for ≥3 days in patients who were receiving oral glucocorticoids), hospitalization, or an emergency department visit.

Secondary end points were the change from baseline to week 52 in the total score on the St. George's Respiratory Questionnaire, with scores ranging from 0 to 100, with higher scores indicating a worse quality of life (minimal clinically important difference [MCID], −4.0)[21]; the change in the score on the Asthma Control Questionnaire–5, with scores ranging from 0 to 6, with higher scores indicating worse asthma control (MCID, −0.5)[22]; the prebronchodilator FEV_1 as assessed according to the American Thoracic Society guidelines[23]; the scores on the asthma nightly and daily symptom diaries, with scores ranging from 0 to 10, with higher scores indicating worse symptoms (MCID, −1.5 for the nightly score and −1.2 for the daily score)[24]; and the annualized rate of exacerbations resulting in hospitalization or an emergency department visit during a 52-week period. Scores on the asthma nightly and daily symptom diaries were included as a secondary end point after trial initiation but before unblinding.

Other outcomes included the time until the first exacerbation and the proportion of patients at 52 weeks who had a reduction from baseline of more than 4 points in the score on the St. George's Respiratory Questionnaire and a reduction of more than 0.5 points in the score on the Asthma Control Questionnaire–5. Additional prespecified end points are summarized in Table S1 in the Supplementary Appendix.

Safety end points included the occurrence of

adverse events, serious adverse events, and adverse events of special interest, along with pharmacodynamics (change from baseline in the blood eosinophil count) and immunogenicity (proportion of patients with binding or neutralizing antibodies).

STATISTICAL ANALYSIS

The analysis of all efficacy end points was performed in the full analysis population, which consisted of all the patients who had undergone randomization in the two trials and received at least one dose of depemokimab or placebo, with the exclusion of patients at sites where concern had been raised about data integrity or violations of Good Clinical Practice guidelines. Safety end points were analyzed in the safety analysis population, in which patients were evaluated according to whether they had received depemokimab or placebo at all protocol-designated times, regardless of their randomized group assignment.

We analyzed the primary end point using a generalized linear model that assumed a negative binomial distribution with covariates of trial group, baseline dose of inhaled glucocorticoids (medium or high), exacerbation history (2, 3, or ≥4 events), geographic region, and baseline prebronchodilator percent of the predicted FEV_1 with an offset of $\log_e$ (total number of years in the trials). In the individual SWIFT-1 and SWIFT-2 trials, we used a fixed-sequence hierarchical testing procedure to control for the type I error for multiplicity arising from the primary and multiple secondary end points, using a step-down closed testing procedure in which the inference for an end point in the predefined hierarchy was dependent on the achievement of statistical significance for the previous end points in the hierarchy (Table S2). The score on the St. George's Respiratory Questionnaire was the first secondary end point that was tested in the hierarchy in each trial. Pooled analyses and subgroup analyses were not controlled for multiplicity.

The widths of confidence intervals have not been adjusted for multiplicity and should not be used for inferential purposes. Additional details about the statistical models, sample-size determination, interim analyses, handling of missing data, and pooled analysis are provided in the Supplementary Appendix.

RESULTS

PATIENT POPULATION

Of the 1285 patients who were screened across both trials, 792 underwent randomization. Of these patients, 762 were included in the full analysis population (382 in SWIFT-1 and 380 in SWIFT-2); 732 patients (367 in SWIFT-1 and 365 in SWIFT-2) completed treatment (Fig. S1B and S1C). Excluded from the full analysis population were 11 patients from one site in SWIFT-1 and 12 patients from two sites in SWIFT-2 because of concerns about data integrity, Good Clinical Practice violations, or both after trial initiation.

The demographic and clinical characteristics of the patients were similar in the two groups at baseline in the two trials (Table 1). Across the two trials and assigned groups, 90% of the patients had a blood eosinophil count of at least 150 cells per microliter at screening. Aside from inhaled glucocorticoids, the most common treatments that were received before treatment were long-acting β_2 agonists and leukotriene-receptor antagonists; during the treatment period, long-acting β_2 agonists and systemic glucocorticoids were the most common (Table S3).

The demographic and clinical characteristics of the patients according to the baseline dose of inhaled glucocorticoids are shown in Table S4. The representativeness of the trial population is described in Table S5.

PRIMARY END POINT

In SWIFT-1, the annualized rate of exacerbations over 52 weeks was significantly lower in patients who received depemokimab (0.46; 95% confidence interval [CI], 0.36 to 0.58) than in those who received placebo (1.11; 95% CI, 0.86 to 1.43), for a rate ratio of 0.42 (95% CI, 0.30 to 0.59) (P<0.001) (Table 2). In SWIFT-2, the annualized rate of exacerbations was also significantly lower in the depemokimab group than in the placebo group, with an annualized rate of 0.56 (95% CI, 0.44 to 0.70) with depemokimab and 1.08 (95% CI, 0.83 to 1.41) with placebo, for a rate ratio of 0.52 (95% CI, 0.36 to 0.73) (P<0.001). In the pooled analysis, the annualized rate of exacerbations was 0.51 (95% CI, 0.43 to 0.60) with depemokimab and 1.11 (95% CI, 0.92 to 1.33) with placebo, for a rate ratio of 0.46 (95% CI, 0.36 to 0.59).

SECONDARY END POINTS

In SWIFT-1, the mean change from baseline in the total score on the St. George's Respiratory Questionnaire at week 52 was −13.03 (95% CI, −15.22 to −10.84) with depemokimab and −9.67 (95% CI, −12.71 to −6.64) with placebo, with negative scores indicating a better quality of life. In SWIFT-2, the mean change from baseline in the score was −14.80 (95% CI, −16.85 to −12.75) with depemokimab and −12.49 (−15.36 to −9.63) with placebo (Table 2 and Fig. S2). At week 52, the between-group difference in the change in score (depemokimab minus placebo) was −3.36 (95% CI, −7.11 to 0.39; P=0.08) in SWIFT-1 and −2.31 (95% CI, −5.84 to 1.23; P=0.20) in SWIFT-2; the difference in the pooled analysis was −2.88 (95% CI, −5.43 to −0.32) (Table 2). Because the between-group difference for this analysis in the individual trials was not significant, the multiplicity hierarchy was broken. As such, no statistical inference can be made on the remaining secondary end points in the hierarchy. Results for the rest of the secondary end points are presented in Table 2 and in Figures S2 through S5.

OTHER OUTCOMES

In SWIFT-1, asthma exacerbations occurred in 32% of the patients in the depemokimab group (81 patients with 124 events) and in 46% of those in the placebo group (61 patients with 151 events). In SWIFT-2, exacerbations occurred in 32% of the patients in the depemokimab group (81 patients with 159 events) and in 50% of those in the placebo group (64 patients with 167 events). These analyses included data that were collected during the treatment period and after the week 52 visit or withdrawal from the trial.

An analysis of the time until the first exacerbation showed a probability that patients in the depemokimab group would have an exacerbation event over the 52-week trial of 32% (95% CI, 27 to 38) in SWIFT-1, 33% (95% CI, 27 to 39) in SWIFT-2, and 32% (95% CI, 28 to 37) in the pooled analysis. In the placebo group, the probability of exacerbation was 47% (95% CI, 39 to 56) in SWIFT-1, 51% (95% CI, 42 to 60) in SWIFT-2, and 49% (95% CI, 43 to 55) in the pooled analysis, for a hazard ratio of 0.56 (95% CI, 0.40 to 0.79) in SWIFT-1, 0.53 (95% CI, 0.38 to 0.74) in SWIFT-2, and 0.54 (95% CI, 0.43 to 0.69) in the pooled analysis (Fig. 1A and 1B).

Data regarding the percentage of patients with a reduction from baseline of more than 4 points in the score on St. George's Respiratory Questionnaire and a reduction of more than 0.5 points in the score on the Asthma Control Questionnaire–5 are provided in Table S6. Results for additional prespecified end points are summarized in Tables S7 through S19.

SUBGROUP ANALYSES

The results of prespecified subgroup analyses of the primary end point in the pooled-data population are shown in Figure 2. A post hoc subgroup analysis showed an annualized rate of exacerbations of 0.35 (95% CI, 0.23 to 0.54) in the depemokimab group and 0.67 (95% CI, 0.37 to 1.19) in the placebo group for patients with a baseline blood eosinophil count of less than 150 cells per microliter (rate ratio, 0.53; 95% CI, 0.25 to 1.09); an annualized rate of 0.58 (95% CI, 0.43 for 0.78) in the depemokimab group and 1.06 (95% CI, 0.77 to 1.46) in the placebo group for those with a cell count of 150 to less than 300 (rate ratio, 0.54; 95% CI, 0.35 to 0.84); an annualized rate of 0.66 (95% CI, 0.49 to 0.89) in the depemokimab group and 0.74 (95% CI, 0.49 to 1.12) in the placebo group for those with a cell count of 300 to less than 500 (rate ratio, 0.89; 95% CI, 0.53 to 1.49); and an annualized rate of 0.45 (95% CI, 0.33 to 0.59) in the depemokimab group and 1.57 (95% CI, 1.17 to 2.12) in the placebo group for those with a cell count of 500 or more (rate ratio, 0.28; 95% CI, 0.19 to 0.42) (Fig. S6).

In the prespecified Chinese subpopulation in SWIFT-1, the annualized rate of exacerbations was 0.32 (95% CI, 0.18 to 0.58) in the depemokimab group and 2.08 (95% CI, 1.35 to 3.21) in the placebo group (rate ratio, 0.15; 95% CI, 0.07 to 0.33) (Table S20). Additional post hoc subgroup analyses, including assessment according to patients' characteristics at baseline and geographic region, are shown in Figure S6 and described in the Supplementary Appendix.

SAFETY

Key safety end points are summarized in Table 3. The proportion of patients with any adverse event was similar in the depemokimab group and the placebo group in SWIFT-1 (73% for both) and SWIFT-2 (72% and 78%, respectively). There were

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	SWIFT-1		SWIFT-2	
	Depemokimab (N=250)	Placebo (N=132)	Depemokimab (N=252)	Placebo (N=128)
Age				
Mean	54.1±13.8	53.6±14.9	53.6±16.0	51.2±16.6
Distribution — no. (%)				
12–17 yr	3 (1)	5 (4)	12 (5)	10 (8)
18–64 yr	185 (74)	91 (69)	169 (67)	93 (73)
≥65 yr	62 (25)	36 (27)	71 (28)	25 (20)
Female sex — no. (%)	144 (58)	79 (60)	160 (63)	81 (63)
Race — no. (%)†				
White	207 (83)	109 (83)	181 (72)	91 (71)
Other	43 (17)	23 (17)	71 (28)	37 (29)
Duration of asthma — yr	22.5±16.1	20.0±16.3	25.6±18.7	24.1±17.9
Age at asthma onset — yr	31.6±18.7	33.5±18.9	28.0±20.9	27.0±21.6
Glucocorticoid use				
Inhaled dose — no. (%)‡				
Medium	118 (47)	61 (46)	94 (37)	60 (47)
High	132 (53)	71 (54)	158 (63)	68 (53)
Maintenance oral dose — no. (%)	8 (3)	13 (10)	13 (5)	6 (5)
Daily oral dose — mg§	6.9±2.6	8.5±5.2	5.7±2.8	6.7±3.0
Peripheral-blood eosinophil count — no. (%)				
≥150 cells/μl at screening	224 (90)	123 (93)	219 (87)	118 (92)
≥300 cells/μl in 12 mo before screening	127 (51)	61 (46)	151 (60)	66 (52)
Blood eosinophil count — cells/μl	298	310	339	330
Total IgE — U/ml	144.4	180.4	158.3	189.3
FEV_1				
Prebronchodilator — liter	1.9±0.7	1.8±0.7	1.8±0.7	1.8±0.7
Prebronchodilator percent predicted	62.3±14.5	60.8±16.6	62.5±16.0	60.9±15.7
Reversibility — %	16.5±15.3	17.9±15.3	17.6±17.5	19.4±17.3
Score on Asthma Control Questionnaire–5¶	2.22±1.12	2.34±1.10	2.20±1.07	2.13±1.00
No. of asthma exacerbations				
Leading to use of oral or systemic glucocorticoids in ≤12 mo — no.(%)				
0	1 (<1)	0	0	0
1	0	0	0	0
2	210 (84)	118 (89)	188 (75)	90 (70)
3	32 (13)	9 (7)	36 (14)	17 (13)
4	2 (1)	3 (2)	14 (6)	7 (5)
>4	5 (2)	2 (2)	14 (6)	14 (11)

Table 1. (Continued)

Characteristic	SWIFT-1		SWIFT-2	
	Depemokimab (N=250)	Placebo (N=132)	Depemokimab (N=252)	Placebo (N=128)
Leading to hospitalization in ≤12 mo — no. (%)				
0	233 (93)	125 (95)	233 (92)	111 (87)
1	13 (5)	4 (3)	6 (2)	12 (9)
≥2	4 (2)	3 (2)	13 (5)	5 (4)
Nasal polyps — no. (%)				
Previous	42 (17)	15 (11)	38 (15)	18 (14)
Current	25 (10)	10 (8)	24 (10)	13 (10)

* Plus–minus values are means ±SD. FEV_1 denotes forced expiratory volume in 1 second.
† Race was reported by the patients. Other races include Black, Asian, and mixed-race patients, along with ethnic groups of American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander.
‡ Categories of inhaled glucocorticoid use are based on the 2021 guidelines of the Global Initiative for Asthma.
§ Data are listed as the prednisolone-equivalent dose. For patients who were receiving maintenance systemic glucocorticoids, a doubling of the existing maintenance dose for at least 3 days was required for the measurement of exacerbations as part of the primary end point.
¶ Scores on the Asthma Control Questionnaire–5 range from 0 to 6, with higher scores indicating worse asthma control (minimal clinically important difference, –0.5).

no deaths and no serious adverse events that were considered by the investigator to be related to depemokimab or placebo. In SWIFT-1, a greater proportion of patients in the depemokimab group than in the placebo group had an adverse event that was categorized as influenza, although none of these events were considered by the investigator to be related to depemokimab or placebo; in SWIFT-2, the proportion of patients with influenza was higher in the placebo group (Table S21). The proportion of patients with nasopharyngitis was lower in the depemokimab groups in each trial (12% and 13%, respectively) than in the placebo groups (19% and 21%, respectively). Details regarding the incidence and relative risk of adverse events of special interest during and after the treatment period are provided in Table S22. There were no meaningful differences between the two groups with respect to laboratory and electrocardiogram results.

In the depemokimab groups, five patients met the criteria for discontinuation according to liver values (alanine aminotransferase [ALT] level of ≥3 times the upper limit of the normal range [ULN] plus a bilirubin level of ≥2 times the ULN or an international normalized ratio [INR] of >1.5, an ALT level of ≥8 times the ULN, or an ALT level of ≥3 times but <8 times the ULN in a patient who was not available for follow-up liver tests). Of these patients, three were enrolled in SWIFT-1 and two in SWIFT-2. All five discontinuation events were considered by the investigator to be unrelated to depemokimab. Among the three patients in SWIFT-1 who met the discontinuation criteria because of abnormal liver values, serious adverse events involving hepatitis A, cholelithiasis, and cholestatic jaundice and an adverse event involving an increased level of ALT were reported. In SWIFT-2, of the two patients who discontinued depemokimab, one was reported to have a serious adverse event involving abnormal ALT and bilirubin levels and an adverse event involving cholelithiasis and increased levels of ALT, aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transferase, and blood bilirubin; the other patient was reported to have an adverse event involving hepatitis E. Most liver-related adverse events, including serious adverse events, had resolved by the follow-up visit, and the remainder were reported as resolving.

PHARMACODYNAMICS AND IMMUNOGENICITY

Rapid and sustained reductions from baseline in the blood eosinophil count were observed among patients receiving depemokimab in both trials, with an 83% reduction in SWIFT-1 and an 82%

Table 2. Summary of Primary and Secondary End Points.*

End Point	SWIFT-1			SWIFT-2			Pooled Trials	
	Depemokimab (N=250)	Placebo (N=132)	P Value†	Depemokimab (N=252)	Placebo (N=128)	P Value†	Depemokimab (N=502)	Placebo (N=260)
Primary end point								
Annualized rate of exacerbations at 52 wk (95% CI)	0.46 (0.36 to 0.58)	1.11 (0.86 to 1.43)	<0.001	0.56 (0.44 to 0.70)	1.08 (0.83 to 1.41)	<0.001	0.51 (0.43 to 0.60)	1.11 (0.92 to 1.33)
Rate ratio (95% CI)	0.42 (0.30 to 0.59)			0.52 (0.36 to 0.73)			0.46 (0.36 to 0.59)	
Percent between-group difference in annual rate (95% CI)	58 (41 to 70)			48 (27 to 64)			54 (41 to 64)	
No. of exacerbations‡	120	150		153	167		273	317
Secondary end points								
Change from baseline in SGRQ score at 52 wk§	−13.03±1.11	−9.67±1.54	0.08	−14.80±1.04	−12.49±1.46	0.20	−13.92±0.76	−11.04±1.06
Treatment difference (95% CI)	−3.36 (−7.11 to 0.39)			−2.31 (−5.84 to 1.23)			−2.88 (−5.43 to −0.32)	
Change from baseline in ACQ-5 score at 52 wk¶	−0.82±0.07	−0.77±0.09		−0.81±0.07	−0.70±0.09		−0.81±0.05	−0.73±0.06
Treatment difference (95% CI)	−0.04 (−0.27 to 0.18)			−0.11 (−0.33 to 0.11)			−0.08 (−0.24 to 0.07)	
Change from baseline in prebronchodilator FEV_1 at 52 wk — liter	0.16±0.03	0.16±0.04		0.24±0.03	0.18±0.04		0.20±0.02	0.17±0.03
Treatment difference (95% CI)	−0.01 (−0.089 to 0.088)			0.06 (−0.04 to 0.15)			0.03 (−0.04 to 0.09)	
Change from baseline in asthma nightly symptom diary at 52 wk‖	−1.39±0.12	−1.30±0.17		−1.18±0.09	−0.97±0.13		NA	
Treatment difference (95% CI)	−0.09 (−0.50 to 0.31)			−0.21 (−0.52 to 0.09)				
Change from baseline in asthma daily symptom diary at 52 wk‖	−1.33±0.10	−1.25±0.14		−1.13±0.08	−0.93±0.11		NA	
Treatment difference (95% CI)	−0.08 (−0.42 to 0.26)			−0.21 (−0.48 to 0.07)				
Annualized rate of exacerbations leading to hospitalization or ED visit at 52 wk (95% CI)**	NA			0.05 (0.02 to 0.09)	0.11 (0.05 to 0.22)		0.02 (0.01 to 0.04)	0.09 (0.05 to 0.15)
Rate ratio (95% CI)	NA			0.42 (0.16 to 1.13)			0.28 (0.13 to 0.61)	
Percent reduction in annual rate (95% CI)	NA			58 (−13 to 84)			72 (39 to 87)	
Number of exacerbations	5	13		16	18		21	31

reduction in SWIFT-2 relative to baseline at week 52 (Fig. S7). On the basis of each patient's worst postbaseline result, antibodies to depemokimab developed in 12% of the patients in SWIFT-1 and in 5% of those enrolled in SWIFT-2 (Table S23). Two patients in SWIFT-2 tested positive for neutralizing antibodies against depemokimab.

DISCUSSION

In the phase 3A SWIFT-1 and SWIFT-2 replicate trials, we investigated the efficacy and safety of depemokimab, an ultra-long-acting anti–interleukin-5 biologic therapy, in patients with severe asthma. Depemokimab, which was administered every 6 months for 52 weeks, was associated with significant reductions in the annual rate of exacerbations in the two trials. Findings appeared to be generally consistent among subgroups and subpopulations. A clear relationship between the efficacy of depemokimab and the blood eosinophil count at baseline was not evident in our trials, although such an association was suggested in earlier randomized, controlled trials of shorter-acting anti–interleukin-5 biologic therapies.[13,18] Our ability to determine such an effect was limited by the requirement that patients who had a blood eosinophil count of fewer than 150 cells per microliter at baseline needed to have had an eosinophil count of at least 300 cells per microliter within the previous year, along with the relatively low exacerbation rate in patients with an eosinophil count of 300 to fewer than 500 cells per microliter.

In the two SWIFT trials, depemokimab had an acceptable safety profile, with a frequency of adverse events that was similar to that in the placebo group. No serious adverse events or deaths were considered by the investigator to be related to depemokimab. These findings add to the existing safety data from our phase 1 trial.[19] In SWIFT-1 and SWIFT-2, stopping criteria that were based on liver measurements were met by five patients in the depemokimab groups. However, among these patients, no liver-related event or associated adverse event or serious adverse event was considered by investigators to be related to depemokimab, and all events were reported as "resolved" or "resolving" by the follow-up visit. A low level of binding antibodies was detected, and only two patients across both trials tested positive for the presence of neutralizing antibodies.

* Plus–minus values are least-squares means ±SE. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used for inferential purposes. NA denotes not applicable.

† For secondary end points, P values are not presented for end points in the multiplicity hierarchy after the calculation of the first nonsignificant P value. No hierarchy or multiplicity adjustment was performed in the pooled analysis, so no P values are reported.

‡ In SWIFT-1, 169 patients (68%) in the depemokimab group had no exacerbations during the on-treatment and post-treatment periods as compared with 71 patients (54%) in the placebo group; in SWIFT-2, the corresponding numbers were 171 patients (68%) and 64 patients (50%).

§ Scores on the St. George's Respiratory Questionnaire (SGRQ) range from 0 to 100, with higher scores indicating a worse quality of life (minimal clinically important difference [MCID], −4.0).

¶ Scores on the Asthma Control Questionnaire–5 (ACQ-5) range from 0 to 6, with higher scores indicating worse asthma control (MCID, −0.5).

‖ Scores on the nightly and daily symptom diaries range from 0 to 10, with higher scores indicating worse symptoms (MCID, −1.5 for the nightly score and −1.2 for the daily score).

Pooled analyses of these data were not performed.

** In line with the statistical analysis plan, the annualized rate of exacerbations leading to hospitalization or an emergency department (ED) visit was not calculated in SWIFT-1 because fewer than 20 such exacerbations occurred. However, the pooled analysis included the number of events from both trials to calculate the annualized rate.

Our findings add to previous data showing that biologic therapies targeting interleukin-5 or its receptor (e.g., mepolizumab, reslizumab, and benralizumab) improve patient outcomes.[11-15] Previous phase 3 trials of biologic therapies have shown reductions in the frequency of exacerbations in patients with asthma ranging from 17 to 59%, as evaluated in different patient populations and with dosing schedules ranging from 4 to 8 weeks.[14,16-18] Our findings regarding depemokimab represent a potential advance in patient quality of life because therapies that have a reduced dosing frequency are associated with a lower patient-reported treatment burden in those with long-term conditions, along with an expected reduction in health care use.[25]

The effect of depemokimab on exacerbations was not associated with a significant effect on

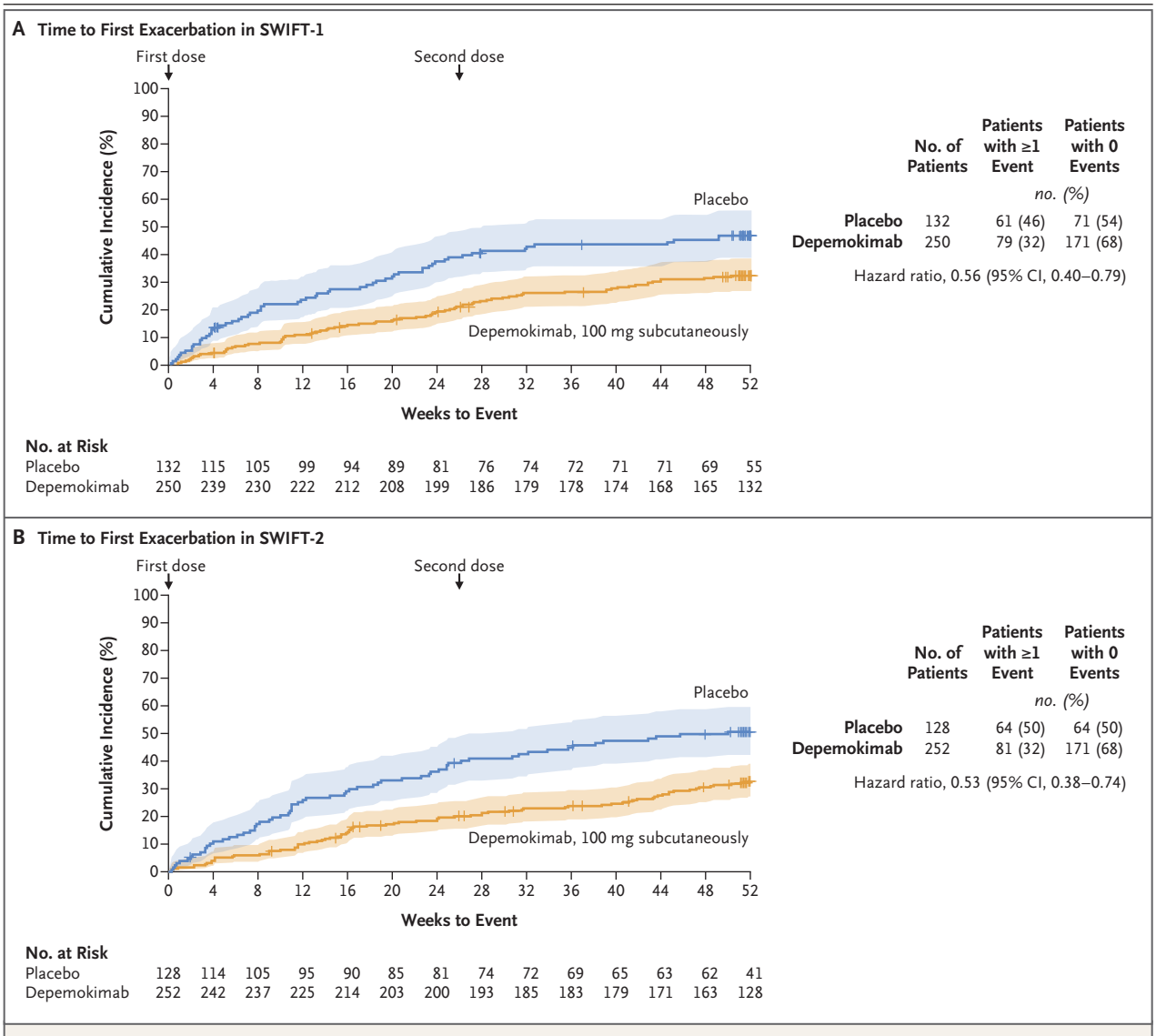

Figure 1. Kaplan–Meier Analysis of the First Asthma Exacerbation.

Shown are the results of analyses performed with the use of a Cox proportional-hazards model in the SWIFT-1 trial (Panel A) and SWIFT-2 trial (Panel B). The covariates in these trials were the assigned group, baseline dose of inhaled glucocorticoids (medium or high), exacerbation history according to the number of events, geographic region, and baseline prebronchodilator percent of the predicted forced expiratory volume in 1 second. The proportional-hazards assumption was met for these analyses. The shaded areas indicate 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used for inferential purposes.

quality of life, according to the score on the St. George's Respiratory Questionnaire. A similar disconnect between exacerbation reduction and changes in patient-reported and symptom-based outcomes has been seen with shorter-acting biologic therapies targeting interleukin-5 and the interleukin-5 receptor,[13,17] although treatment effects on these outcomes have been seen with most earlier studies.[14,17,18,26] Potential explanations include the consideration that mechanisms driving these different outcomes are distinct to some extent and change over time in patients with severe asthma who are recruited to participate in clinical trials, because an increasing number of patients have received previous biologic therapy. Consistent with this hypothesis is the large reduction of 85% in the exacerbation rate with depemokimab in the Chinese subpopulation in SWIFT-1, in which many of the patients with severe asthma were unlikely to have received previous biologic therapy.[27] The relatively low exacerbation rate in the placebo group as compared with the previous year highlights the challenges in conducting trials of biologic therapies involving patients with severe asthma, because not all patients with asthma that is considered to be "difficult to

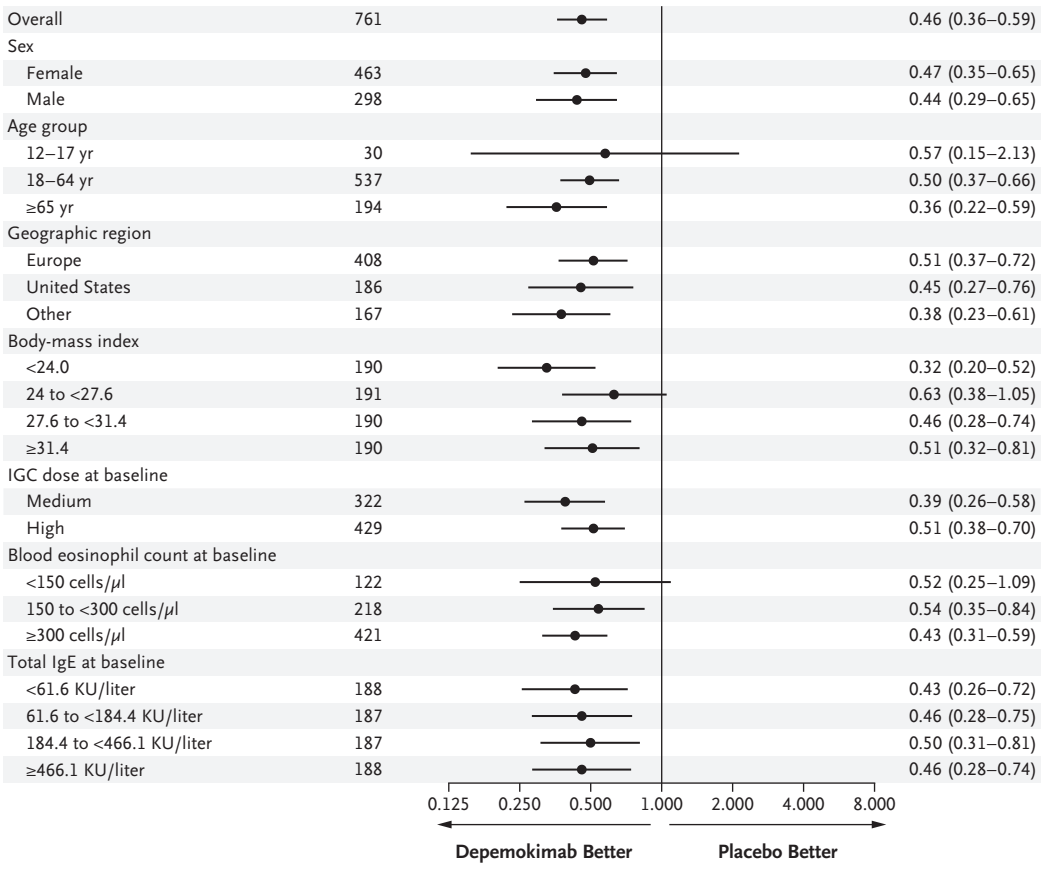

Figure 2. Subgroup Analysis of the Primary End Point.

Shown is the annualized rate of asthma exacerbations (the primary end point) during a 52-week period in pooled data from the SWIFT-1 and SWIFT-2 trials, according to subgroup. Only subgroups with at least 20 patients were included in the statistical analysis. A post hoc subgroup analysis according to body-mass index (the weight in kilograms divided by the square of the height in meters) is included in place of the prespecified analysis according to weight. Definitions of the inhaled glucocorticoid (IGC) dose are based on the 2021 guidelines of the Global Initiative for Asthma. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used for inferential purposes.

Table 3. Adverse Events.

Event	SWIFT-1		SWIFT-2	
	Depemokimab (N=250)	Placebo (N=132)	Depemokimab (N=251)	Placebo (N=129)*
Any adverse event — no. (%)	183 (73)	97 (73)	180 (72)	101 (78)
Related to depemokimab or placebo†	8 (3)	5 (4)	11 (4)	1 (1)
Leading to permanent discontinuation or withdrawal from trial	3 (1)	2 (2)	2 (1)	1 (1)
Leading to dose interruption or delay	1 (<1)	0	0	0
Serious adverse event — no. (%)‡	15 (6)	22 (17)	19 (8)	13 (10)

* In SWIFT-2, one patient who was assigned to the depemokimab group received placebo and was therefore included in the placebo group for safety analyses in line with the predefined analysis sets.
† The determination that an adverse event was related to depemokimab or placebo was made by the investigator.
‡ No serious adverse events were considered by the investigator to be related to depemokimab or placebo, and no serious adverse events resulted in death.

treat" have severe asthma requiring escalation to biologic therapy.[28] In addition, it should be noted that adherence to standard care was not monitored in the SWIFT trials.

A further limitation of these trials is that SWIFT-1 was initiated during the coronavirus disease 2019 pandemic, which potentially had an effect on the overall rate of exacerbations[29] and the ability to conduct routine lung-function testing.[30] Moreover, the two trials were conducted across multiple regions, with a corresponding potential for variability in standard care. A small number of adolescents were included in the trials, which limits the assessment of efficacy and safety among this important subpopulation. Also, we did not evaluate the level of exhaled nitric oxide, because the benefits of biologic therapy targeting interleukin-5 have previously been shown to be independent of this measure.[31] However, the lack of data regarding exhaled nitric oxide limits the ability to ascertain the efficacy of depemokimab in patients with different T2 biomarker combinations. Finally, although a history of interleukin-5 therapy during the 12 months before screening was an exclusion criterion, we did not collect earlier data regarding exposure to biologic therapy or the rationale for not continuing such therapy. Additional studies involving patients with severe asthma that capture the quantifiable variables described above are clearly indicated.

Our data showed that the administration of depemokimab every 6 months reduced the annualized rate of exacerbations among patients with severe asthma with an eosinophilic phenotype.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

The authors' affiliations are as follows: Guy's Severe Asthma Centre, Guy's and St. Thomas' NHS Foundation Trust, and the School of Immunology and Microbial Sciences, King's College London (David J. Jackson), Barts Health NHS Trust (P.E.P.), and GSK (L.J., N.B., S.S., P.H.), London, and the Oxford Respiratory NIHR Biomedical Research Centre, Nuffield Department of Clinical Medicine, University of Oxford, Oxford (I.D.P.) — all in the United Kingdom; National Jewish Health, Denver (M.E.W.); the University of Wisconsin–Madison, Madison (Daniel J. Jackson); the University of Cincinnati College of Medicine and Bernstein Clinical Research Center, Cincinnati (D.B.); Clinical Research Center, Respiratory Medicine, IKF Pneumologie Mainz, Mainz, and Thoraxklinik Heidelberg, Heidelberg — both in Germany (S.K.); State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Joint International Research Laboratory of Respiratory Health, Guangzhou Institute of Respiratory Health, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China (R.C.); Fukushima Medical University, Fukushima, Japan (J.S.); Hospital Vithas Xanit Internacional, Málaga, Spain (G.L.M.); Centrum Medyczne Lucyna Andrzej Dymek, Strzelce Opolskie, Poland (L.D.); and GSK, Collegeville, PA (D.S.).

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