Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial

Claus Bachert, PhD,[a,b] Ana R. Sousa, PhD,[c] Valerie J. Lund, MD,[d] Glenis K. Scadding, MD,[d] Philippe Gevaert, MD,[a] Shuaib Nasser, MD,[e] Stephen R. Durham, MD,[f] Marjolein E. Cornet, MD,[g] Harsha H. Kariyawasam, PhD,[d] Jane Gilbert, MSc,[h] Daren Austin, PhD,[c] Aoife C. Maxwell, PhD,[i] Richard P. Marshall, PhD,[c] and Wytske J. Fokkens, PhD[g]

Ghent, Belgium; Stockholm, Sweden; Uxbridge, London, and Cambridge, United Kingdom; and Amsterdam, The Netherlands

Background: Patients with eosinophilic nasal polyposis frequently require surgery, and recurrence rates are high.
Objective: We sought to assess the efficacy and safety of mepolizumab versus placebo for severe bilateral nasal polyposis.
Methods: This randomized, double-blind, placebo-controlled trial recruited patients aged 18 to 70 years with recurrent nasal polyposis requiring surgery. Patients received 750 mg of intravenous mepolizumab or placebo every 4 weeks for a total of 6 doses in addition to daily topical corticosteroid treatment. The primary end point was the number of patients no longer requiring surgery at Week 25 based on a composite end point of endoscopic nasal polyp score and nasal polyposis severity visual analog scale (VAS) score. Secondary end points included change in nasal polyposis severity VAS score, endoscopic nasal polyp score, improvement in individual VAS symptoms (rhinorrhea, mucus in throat, nasal blockage, and sense of smell), patient-reported outcomes, and safety.
Results: One hundred five patients received mepolizumab (n = 54) or placebo (n = 51). A significantly greater proportion of patients in the mepolizumab group compared with the placebo group no longer required surgery at Week 25 (16 [30%] vs 5 [10%], respectively; $P = .006$). There was a significant improvement in nasal polyposis severity VAS score, endoscopic nasal polyp score, all individual VAS symptom scores, and Sino-Nasal Outcome Test patient-reported outcome score in the mepolizumab compared with placebo groups. Mepolizumab's safety profile was comparable with that of placebo.
Conclusion: In patients with recurrent nasal polyposis receiving topical corticosteroids who required surgery, mepolizumab treatment led to a greater reduction in the need for surgery and a greater improvement in symptoms than placebo. (J Allergy Clin Immunol 2017;140:1024-31.)

Key words: *Nasal polyposis, mepolizumab, IL-5, eosinophil, chronic rhinosinusitis*

Chronic rhinosinusitis is common, with a prevalence of 11% in Europe.[1] It can be categorized into 2 phenotypes based on results from nasal endoscopy and computed tomography: chronic rhinosinusitis with nasal polyps and chronic rhinosinusitis without nasal polyps.[2] Up to 4% of the general population is estimated to be affected by nasal polyps.[3] Nasal polyps often have a negative effect on numerous aspects of quality of life (QoL), including physical health, general health, social functioning, sleep, and mental health,[4] and can lead to workplace absenteeism.[5] Symptoms experienced by patients with nasal polyposis include nasal blockage, loss of smell, rhinorrhea, and symptoms derived from lower airway involvement.[4]

Current treatment options for patients with nasal polyposis are limited to intranasal and oral corticosteroids, long-term antibiotics, and surgery.[6-8] Intranasal corticosteroids are usually the initial treatment option for nasal polyps, with good results for patients with mild disease.[9] Short-term courses of systemic corticosteroids are reserved for more severe cases.[10]

Although symptoms can be controlled medically in some patients, surgery is often required.[7] Surgery can range from a simple polypectomy to full removal of polypoid mucosal tissue

From [a]the Upper Airways Research Laboratory and Department of Oto-Rhino-Laryngology, Ghent University and Ghent University Hospital; [b]the Division of ENT Diseases, CLINTEC, Karolinska Institute, University of Stockholm; [c]the Respiratory Therapy Unit, [h]Clinical Statistics, and [i]Respiratory Clinical Sciences & Operations, GlaxoSmithKline, Stockley Park, Uxbridge; [d]the Royal National Throat, Nose and Ear Hospital, UCLH London; [e]the Department of Allergy, Cambridge University Hospitals NHS Foundation Trust, Cambridge; [f]Allergy and Clinical Immunology, National Heart and Lung Institute, Imperial College London; and [g]the Department of Otorhinolaryngology, Academic Medical Center, Amsterdam.

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Corresponding author: Claus Bachert, PhD, Universitair Ziekenhuis Gent, Upper Airway research Laboratory, De Pintelaan 185, Ghent B-9000, Belgium. E-mail: Claus.Bachert@UGent.be.

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Abbreviations used
AE: Adverse event
ECG: Electrocardiography
EQ-5D: EuroQual 5-Dimensions
FVC: Forced vital capacity
ITT: Intent-to-treat
PEFR: Peak expiratory flow rate
PK: Pharmacokinetics
PnIF: Peak nasal inspiratory flow
QoL: Quality of life
SNOT-22: Sino-Nasal Outcome Test
VAS: Visual analog scale

from sinuses.[7] The recurrence rate is impactful for patients, and repeated surgery is often required; one study found that 15% of patients had 4 to 6 procedures within an 8-year period.[11] Furthermore, long-term follow-up and treatment with topical corticosteroids is usually still required after surgery.[12] There is also a proportion of patients for whom surgery, oral corticosteroids, or both fail to achieve disease control.

IL-5 is the critical factor that promotes eosinophil development and survival.[13,14] Mepolizumab, an IL-5 antibody, is under investigation as a treatment for nasal polyposis.[15] Mepolizumab reduces blood and tissue eosinophil counts[16,17] and is approved for the treatment of severe eosinophilic asthma. Both severe eosinophilic asthma and nasal polyposis are characterized by prominent local eosinophilic inflammation.[18] IL-5 appears to have a key role in the pathogenesis of nasal polyposis: (1) nasal polyps are associated with IL-5 expression[18-21]; (2) the expression of IL-5 within nasal polyp tissue has been associated with asthma comorbidity[22]; and (3) eosinophilic inflammation is associated with polyp recurrence after surgery.[23] Consequently, IL-5 is a major target for therapeutic intervention, and previous studies with small numbers of patients have shown that inhibiting IL-5 with anti–IL-5 treatments, such as mepolizumab, can successfully reduce nasal polyp size.[15,24]

The aim of this study was to build on previous studies and determine whether mepolizumab treatment could reduce the need for surgery in patients with severe recurrent bilateral nasal polyposis. This was assessed by using a novel composite end point of polyp size and symptom severity.

METHODS

Study design and oversight

This was a 1:1 randomized, double-blind, placebo-controlled, multicenter study (NCT01362244, EudraCT: 2008-003772-21, GSK study ID: 111782). Six centers across 3 countries (Belgium, Netherlands, and the United Kingdom) took part in the study between May 2009 and December 2014. Further details of the investigators and methods can be found in the Methods section in this article's Online Repository at www.jacionline.org. Initially, the study comprised 2 phases: a treatment phase and a follow-up extension phase. The extension phase was subsequently removed from the protocol because few patients were enrolled in this phase. Although patients were required to have been receiving intranasal steroids for at least 3 months before study entry, to standardize treatment before randomization, patients received intranasal steroids (fluticasone propionate [1 mg/mL], 2 sprays [50 μg per spray] in the morning in each nostril daily [Flixonase Aqueous Nasal Spray; GlaxoSmithKline, Uxbridge, United Kingdom]) for 10 to 14 days (run-in period). Patients were then randomized to receive 750 mg of mepolizumab or placebo by means of intravenous infusion every 4 weeks (Weeks 1, 5, 9, 13, 17, and 21) for 6 doses. Intranasal steroids were continued during the study at the same dose and regimen as used during the run-in period. See the Methods section in this article's Online Repository for randomization and blinding details.

Mepolizumab and placebo were identical in appearance and administered by a staff member who was blinded to the infusion content, unaware of the study randomization, and independent of the study protocol and outcomes. An unblinded pharmacist dispensed the study drugs. The protocol was approved by local ethics committees, and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from participants before the start of any procedures. The protocol for the analysis is available from the GlaxoSmithKline Clinical Study Register (GlaxoSmithKline study ID: 111782).

Patients

Patients were screened for eligibility before (within 28 days) commencing the run-in period. Patients were 18 to 70 years of age with severe recurrent bilateral nasal polyposis and required surgery according to the predefined criteria of an endoscopic nasal polyp score of 3 or more in 1 nostril (and a minimum score of 2 on the other side) and a visual analog scale (VAS) nasal symptom score of greater than 7 (see Table E1 in this article's Online Repository at www.jacionline.org). Patients were also required to be eligible for surgery as a result of being refractory to standard-of-care steroid therapy (received intranasal steroids for ≥3 months and/or received a short course of oral steroids) at the time of enrollment and to have undergone at least 1 previous nasal polyp removal surgery. Exclusion criteria included the requirement for continuous high-dose oral corticosteroids, treatment with other biologics in the past 12 months, or asthma exacerbations requiring hospitalization within 4 weeks of screening.

End points

The primary end point was the number of patients who no longer met the criteria for requiring surgery 4 weeks after the final dose (Week 25) based on endoscopic nasal polyposis scores and nasal polyposis severity VAS scores (see Table E2 in this article's Online Repository at www.jacionline.org). The endoscopic nasal polyposis score was assessed by means of endoscopy for each nostril separately and by using the highest unilateral score. Each nostril was scored from 0 to 4 (0 = no polyps and 4 = large polyps causing almost complete nasal obstruction), according to the criteria in Table E3 in this article's Online Repository at www.jacionline.org. Nasal polyposis severity VAS scores were assessed by asking patients to indicate on a VAS (0-10 cm) the severity of their nasal polyposis, considering how much trouble was caused by each of the following symptoms: rhinorrhea, mucus in the throat, nasal blockage, and loss of smell (see the Methods section in this article's Online Repository for details on the analysis).

Secondary end points were the number of patients who met the criteria for requiring polyposis surgery at each time point, change in nasal polyposis severity VAS score from baseline to Week 25, change in endoscopic nasal polyp score from baseline to Week 25, individual-symptom VAS scores (rhinorrhea, mucus in the throat, nasal blockage, and loss of smell), patient-reported outcomes (Sino-Nasal Outcome Test [SNOT-22] questionnaire and EuroQual 5-Dimensions [EQ-5D] questionnaire), peak nasal inspiratory flow (PnIF), olfaction test results (performed with the Sniffin' Sticks Screening-12 test), lung function assessments (FEV_1, forced vital capacity [FVC], and peak expiratory flow rate [PEFR]), blood eosinophil counts, and pharmacokinetics (PK).

In the Sniffin' Sticks Screening-12 test, patients are presented with 12 different odors in turn and asked to identify the source from a list of 4 options. Patients were blindfolded and performed the test for each nostril separately (with the other blocked with tape). Scores range from 0 to 12 for each nostril.

Safety assessment included adverse events (AEs), vital signs, electrocardiographic (ECG) testing, and clinical laboratory testing.

Statistical analysis

Efficacy was analyzed in the intent-to-treat (ITT) and per-protocol populations; PK and safety were analyzed in the safety population (patients who received ≥1 dose of study drug). The maximum sample size was 110, with

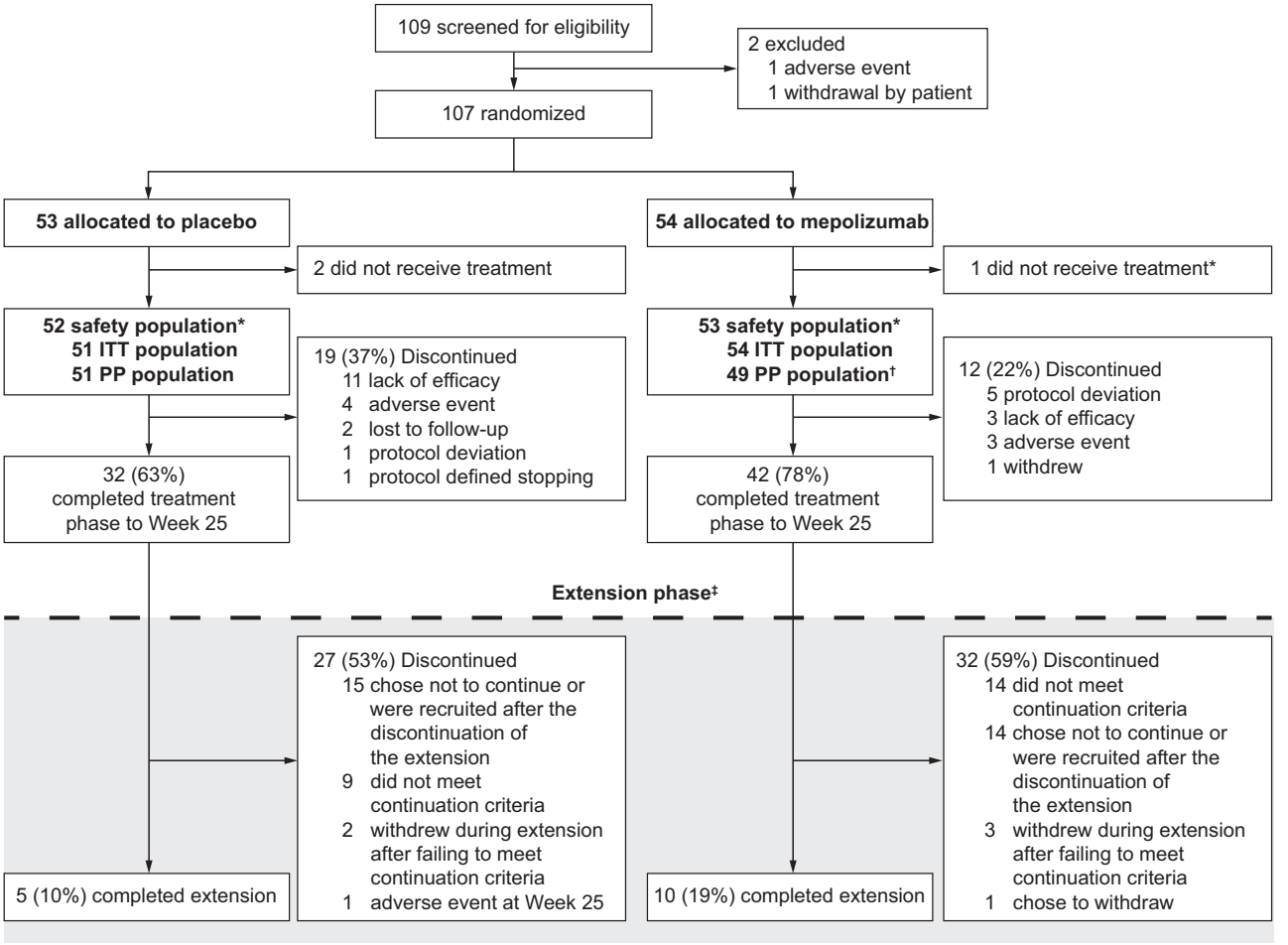

FIG 1. Patient flow through the study. *One patient randomized to the mepolizumab group received placebo in error; this patient is included in the safety population for placebo. †Protocol deviations were incorrect treatment/dose (n = 3), did not meet inclusion criteria (n = 1), and smoked during the study (n = 1). ‡Before a protocol amendment that discontinued recruitment to the extension study, patients were given the option to enter the extension study. Patients were eligible to enter the extension if they were judged to no longer have a requirement for surgery according to the criteria defined in Table E2. Results from the extension phase are not presented because of low patient numbers. *PP*, Per-protocol.

an unblinded sample size re-estimation conducted using "predictive power" when 46 patients completed the study (after applying the stopping rules for efficacy and futility).[25] The predictive power calculation suggested a sample size of 50 patients per treatment arm. For analysis of the primary end point, patients were classified as responders or nonresponders at Week 25 based on the endoscopic nasal polyposis score and nasal polyposis severity VAS score; patients with missing data at Week 25 were considered nonresponders. The Fisher exact test was used for primary end point analysis. Additional *post hoc* analyses were performed on change from baseline in endoscopic polyp scores and blood eosinophil counts. Endoscopic nasal polyp scores and pharmacodynamic data (PnIF, olfaction, FEV_1, FVC, and PEFR) were analyzed by using ordinal logistic regression; other secondary end points were analyzed with mixed-effects modeling.

Role of the funding source

GlaxoSmithKline, in collaboration with the academic clinical investigators, provided input on the design and conduct of the study; oversaw the collection, management, and statistical analysis of data; and contributed to the interpretation of the data and the preparation, review, and submission of the manuscript. All authors had roles in the conception, design, and interpretation of the analysis. All authors participated in the development of the manuscript and had access to the data from the study. The decision to submit for publication was that of the authors alone. The final decision on manuscript submission was made by the authors. The sponsors did not have the right to veto publication.

RESULTS

A total of 107 patients were randomized to receive mepolizumab (n = 54) or placebo (n = 53, Fig 1). The first patient was enrolled on May 12, 2009, and the last patient completed on December 5, 2014. Two randomized patients withdrew before treatment. One patient randomized to receive mepolizumab received a first dose of placebo in error and was withdrawn; this patient was assigned to the placebo group for safety analyses and the mepolizumab group for efficacy analyses (ITT). Therefore the ITT population included 105 patients who received at least 1 dose of mepolizumab or placebo (mepolizumab, 54; placebo, 51). The per-protocol population excluded 5 patients from the mepolizumab group because they did not require surgery after the run-in period (n = 1), repeated cigarette smoking during the study (n = 1), received placebo as their first dose and then withdrew (n = 1), or received placebo as their second dose and withdrew (n = 2). Patients' demographics and characteristics

TABLE I. Patients' baseline demographics and characteristics (ITT population)

Demographics	Placebo (n = 51)	Mepolizumab, 750 mg IV (n = 54)
Age (y), mean (SD)	50 (10)	51 (11)
Sex, no. (%)		
Female	17 (33)	13 (24)
Male	34 (67)	41 (76)
BMI (kg/m^2), mean (SD)	25.1 (3.0)	26.1 (2.7)
Height (cm), mean (SD)	175 (9)	176 (9)
Weight (kg), mean (SD)	77.2 (13.1)	81.1 (10.7)
Ethnicity, n (%)		
Hispanic or Latino	0	0
Not Hispanic or Latino	51 (100)	54 (100)
Race, n (%)		
Asian: Central/South Asian heritage	0	2 (4)
Asian: Japanese/East Asian or South East Asian heritage	1 (2)	0
White	50 (98)	52 (96)
Baseline symptom severity VAS symptom score*		
Nasal polyposis, LS mean (95% CI)	8.55 (7.88-9.23)	8.50 (7.84-9.16)
Rhinorrhea, LS mean (95% CI)	6.19 (5.50-6.87)	6.24 (5.57-6.91)
Mucus in throat, LS mean (95% CI)	6.27 (5.57-6.96)	6.01 (5.34-6.69)
Nasal blockage, LS mean (95% CI)	8.01 (7.32-8.69)	7.90 (7.23-8.56)
Loss of smell, LS mean (95% CI)	9.10 (8.45-9.75)	9.06 (8.43-9.69)
Baseline total endoscopic nasal polyp score, mean (SD)†	6.31 (0.88)	6.28 (0.88)
Baseline SNOT-22 score, mean (SD)‡	49.5 (19.0)	51.5 (17.0)
Baseline EQ-5D		
Index score, mean (SD)§	0.84 (0.20)	0.88 (0.15)
VAS score, mean (SD)‖	67.74 (19.65)	73.30 (17.07)
Baseline PnIF, (L/min), mean (SD)	102 (65)	101 (67)
History of asthma, yes, n (%)¶	38 (75)	44 (81)
Baseline lung function		
FEV_1 (L), mean (SD)	3.27 (0.97)	3.15 (0.98)
FVC (L), mean (SD)	4.45 (1.09)	4.46 (1.14)
PEFR (L/min), mean (SD)	474 (156)	461 (140)

BMI, Body mass index; *IV*, intravenous; *LS*, least squares.
*0- to 10-cm VAS scale (0 = not troublesome and 10 = worst possible).
†*Post hoc* analysis.
‡SNOT-22 scores range from 0 to 110; lower scores imply less severe symptoms.
§Mean score of 5 questions; a score of 1 indicates full health, and lower scores indicate poorer health.
‖0- to 100-mm VAS scale (0 = worst imaginable health state and 100 = best imaginable health state).
¶All patients with asthma had mild or moderate disease.

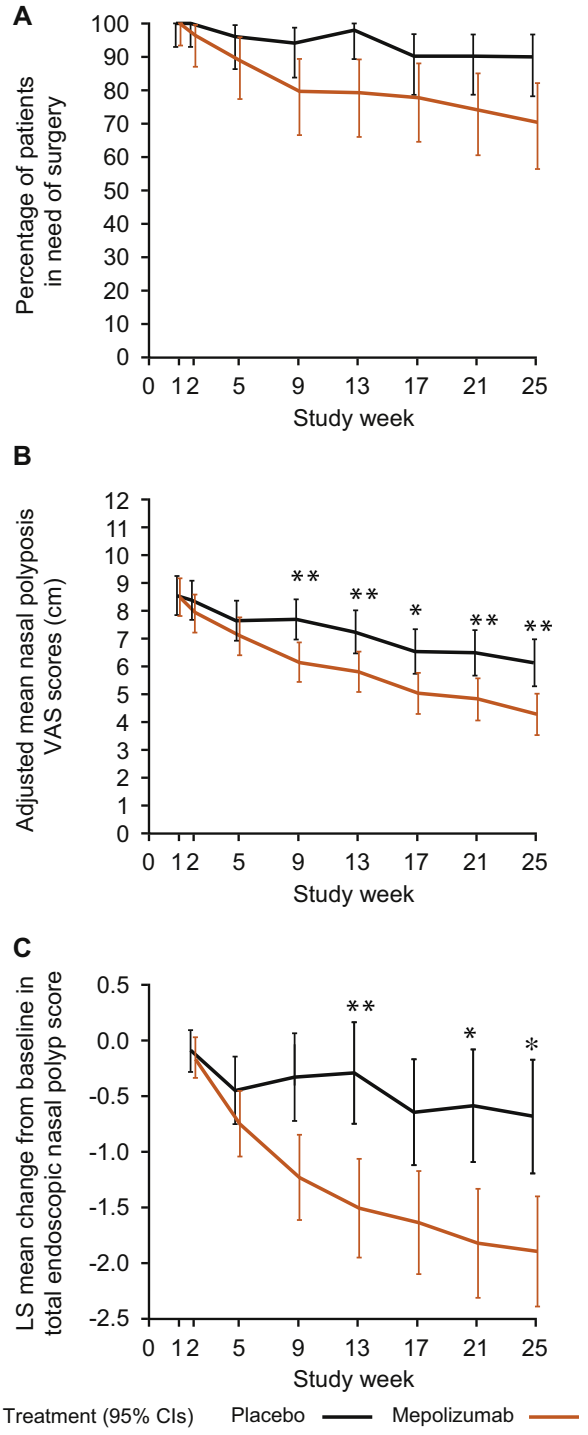

FIG 2. Efficacy. **A,** Percentage of patients meeting the criteria for surgery over time (missing data imputed as nonresponders). **B,** Mean nasal polyposis severity VAS score for nasal polyposis. **C,** Least squares *(LS)* mean change from baseline in total endoscopic nasal polyp score (ITT population [*post hoc* output using last observation carried forward]). *$P \leq .05$ and **$P \leq .01$. *Bars* represent 95% CIs. *VAS*, 0 to 10 cm (0 = not troublesome and 10 = worst possible troublesome).

were well balanced between the treatment groups (Table I). The majority of patients had a history of asthma in both groups; all patients with asthma had mild or moderate disease (Table I).

A significantly greater proportion of patients in the mepolizumab group no longer met the criteria for requiring surgery compared with those in the placebo group at Week 25 (ITT, 16 [30%] vs 5 [10%]; $P = .006$; Fig 2, *A*, and see Table E4 in this article's Online Repository at www.jacionline.org). This effect was observed from Week 9 and maintained until Week 25.

There was a significant improvement in nasal polyposis severity VAS scores in the mepolizumab group compared with the placebo group, with a treatment difference in favor of mepolizumab of −1.8 at Week 25 (ITT 95% CI, −2.9 to −0.8; $P = .001$; Fig 2, *B*, and see Table E4). The probability of having a reduction in endoscopic nasal polyp score was significantly

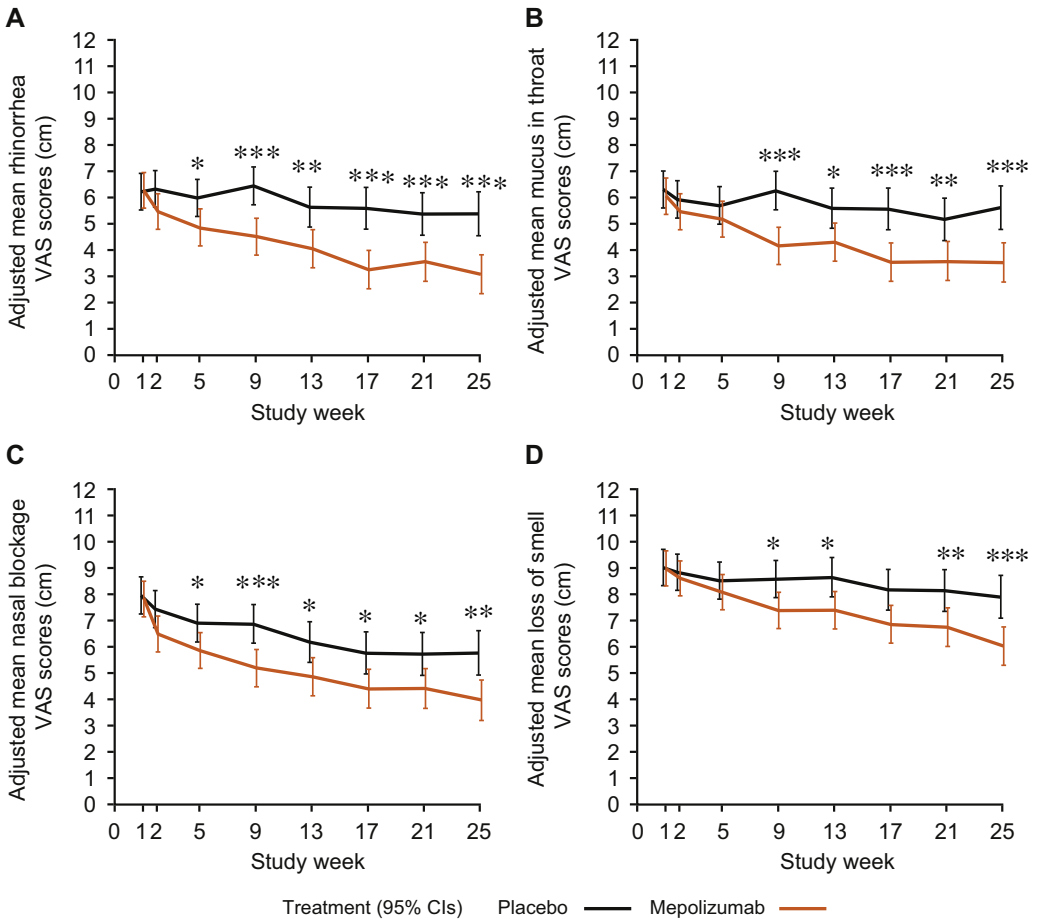

FIG 3. Adjusted mean individual symptom VAS scores over time for rhinorrhea **(A)**, mucus in throat **(B)**, nasal blockage **(C)**, and loss of smell (**D**; ITT population [adjusted for baseline, visit, treatment group, and visit-treatment group interaction]). *Bars* represent 95% CIs. *$P \leq .05$, **$P \leq .01$, and ***$P \leq .001$. *VAS*, 0 to 10 cm (0 = not troublesome and 10 = worst possible troublesome).

higher in the mepolizumab group than in the placebo group from Week 9 (odds ratio for mepolizumab vs placebo, 5.6; 95% CI, 1.2-26.6; $P = .031$) and remained higher at Week 25 (odds ratio, 6.6; 95% CI, 1.3-34.5; $P = .025$). Similarly, a *post hoc* analysis of the mean change from baseline in the total endoscopic nasal polyp score showed a significant difference between the placebo and mepolizumab groups from Week 9 (Fig 2, *C*) to Week 25. In total, 27 (50%) patients receiving mepolizumab and 14 (27%) patients receiving placebo improved by 1 or more points in total endoscopic nasal polyp score (see Table E4). A *post hoc* analysis of patients in the mepolizumab group found there was no association between baseline eosinophil counts and achieving a 1-point or greater improvement in endoscopic nasal polyp score at Week 25 (see Fig E1 in this article's Online Repository at www.jacionline.org); however, it is important to note that numbers were small in this analysis (n = 28 had a ≥1-point improvement in total endoscopic nasal polyp score vs n = 14 with a <1-point improvement).

Mean individual symptom VAS scores (rhinorrhea, mucus in the throat, nasal blockage, and loss of smell) adjusted for baseline, visit, treatment group, and visit–treatment group interaction were significantly improved in the mepolizumab group compared with the placebo group at Week 25 (ITT population, Fig 3 and see Table E5). Statistically significant differences were first observed at Week 5 for rhinorrhea and nasal blockage and Week 9 for mucus and loss of smell; all remained statistically significantly different through Week 25 (ITT population, see Table E6 in this article's Online Repository at www.jacionline.org).

The improvement in mean SNOT-22 questionnaire scores was significantly greater in the mepolizumab group compared with the placebo group (see Fig E2 in this article's Online Repository at www.jacionline.org). SNOT-22 scores improved between Weeks 0 and 25 in the placebo (Week 1, 49.5 [SD, 19.0]; Week 25, 38.2 [24.5]) and mepolizumab (Week 1, 51.5 [17.0]; Week 25, 28.8 [22.0]) groups. At Week 25, the score for the mepolizumab group was statistically significantly lower than for the placebo group (see Table E5).

There were no differences between the mepolizumab and placebo groups in EQ-5D index scores at Week 25, which assessed general QoL not specific to nasal polyposis. Both groups showed increases in mean EQ-5D VAS symptom scores at Week

TABLE II. Summary of treatment-emergent AEs reported in more than 5% of patients in either treatment group (safety population)

AE type	No. (%) of patients	
	Placebo (n = 52)	Mepolizumab, 750 mg IV (n = 53)
All AEs		
On treatment	42 (81)	40 (75)
Drug related*	3 (6)	5 (9)
Led to discontinuation of study drug or withdrawal from the study	6 (12)	3 (6)
SAEs		
Nonfatal	0	0
Fatal	0	0
Any on-treatment AE		
Headache	20 (38)	13 (25)
Nasopharyngitis	12 (23)	10 (19)
Oropharyngeal pain	4 (8)	6 (11)
Back pain	0	5 (9)
Influenza	2 (4)	4 (8)
Arthralgia	3 (6)	3 (6)
Pyrexia	1 (2)	3 (6)
Dyspnea	4 (8)	2 (4)
Nausea	4 (8)	2 (4)
Asthma	3 (6)	2 (4)
Cough	3 (6)	2 (4)
Ear pain	5 (10)	1 (2)
Epistaxis	3 (6)	1 (2)
Fatigue	4 (8)	1 (2)
Insomnia	3 (6)	0
Rhinorrhea	3 (6)	0
Sinus headache	3 (6)	0

SAE, Serious adverse event.
*Investigator's assessment of causality.

25 compared with Week 0; at Week 25, scores were higher in the mepolizumab group compared with the placebo group (see Table E5).

At Week 25, least squares mean PnIF was statistically significantly higher for the mepolizumab group compared with the placebo group (mean difference, 26.7 [95% CI, 3.1-50.2]; $P = .027$; see Tables E5 and E7 in this article's Online Repository at www.jacionline.org). For olfaction, there was a numeric but not statistically significant difference between the mepolizumab and placebo groups in favor of mepolizumab (mean difference, 0.7; 95% CI, −0.5 to 1.9; $P = .233$) at Week 25. For lung function (FEV_1, FVC, and PEFR), there were no statistically significant differences between the mepolizumab and placebo groups at Week 25 (see Table E5), although there were significant differences at other time points in favor of mepolizumab over placebo in FVC and PEFR (see Table E7). A *post hoc* analysis demonstrated that blood eosinophil counts decreased from a geometric mean of 500 cells/μL (SD log, 0.712) at baseline to 50 cells/μL (SD log, 1.134) at Week 25 in the mepolizumab group. Decreases were not seen in the placebo group (see Table E8 in this article's Online Repository at www.jacionline.org). PK results were as expected for 750 mg of mepolizumab administered intravenously (see Table E9 in this article's Online Repository at www.jacionline.org).

The overall incidence of treatment-emergent AEs, AEs considered drug related by the investigator, and AEs leading to treatment discontinuation were similar between the treatment groups (Table II). Details of AEs leading to treatment discontinuation are presented in Table E10 in this article's Online Repository at www.jacionline.org. The most frequently reported AEs were headache and nasopharyngitis, both reported by more patients in the placebo group than in the mepolizumab group. Of the remaining AEs with greater than 5% incidence in either treatment group, oropharyngeal pain, back pain, influenza, and pyrexia were the only events reported by more patients in the mepolizumab group compared with the placebo group. There were no serious AEs reported during the study. In general, clinical laboratory evaluations and vital signs were similar between groups, with no notable trends identified; 11 patients (placebo, 9; mepolizumab, 2) had abnormal clinical chemistry values, and 6 patients (placebo, 3; mepolizumab, 3) had vital sign abnormalities at any point during the study, but these were not reported as AEs. There was also a decrease in mean leukocyte counts in the mepolizumab group from 7.16×10^9/L before dosing to 5.90×10^9/L at Week 9, which was sustained over the course of treatment.

DISCUSSION

This randomized, double-blind, placebo-controlled study aimed to determine whether mepolizumab treatment could reduce the need for surgery in patients with severe, recurrent bilateral nasal polyps receiving topical corticosteroid therapy. Based on a composite end point of reductions in endoscopic nasal polyposis scores and nasal polyposis severity VAS scores, the study demonstrated a statistically significant reduction in the proportion of patients who met the criteria for requiring surgery 4 weeks after the last dose at Week 25 in the mepolizumab group compared with the placebo group. This was supported by clinically significant improvements in symptoms and QoL-related SNOT-22 scores in the mepolizumab group compared with the placebo group. Of note, statistically significant improvements in efficacy outcomes were observed 9 weeks after starting treatment with mepolizumab. The combination of these findings suggests that mepolizumab has a beneficial effect on nasal polyposis and might reduce the need for surgery in patients with refractory nasal polyposis.

The primary goal of treatment for nasal polyps is to achieve and maintain clinical control through a reduction in polyp size and growth, thereby improving symptoms and maintaining a healthy or almost healthy nasal mucosa with local treatment only.[8] Previous studies have shown that systemic steroids improve nasal-related symptom scores for a short time.[8,10] However, their use is limited by the potential long-term side effects of systemic steroids.[26] The current study showed that mepolizumab treatment led to significant improvements in symptom scores (rhinorrhea, mucus in throat, nasal blockage, and loss of smell) during treatment. Efficacy results from this study were consistent with results from the smaller study investigating mepolizumab in the treatment of nasal polyposis.[15] Improvements in endoscopic nasal polyp scores were also comparable with those shown in an initial study using the anti–IL-4/IL-13 therapy dupilumab.[27] Loss of smell was shown to be improved by dupilumab compared with baseline and placebo by using UPSIT,[27] and mepolizumab significantly improved olfaction compared with placebo measured by using the VAS score in the current and the former study.[15] Because different olfaction tests (Sniffin' Sticks

Screening-12 test for mepolizumab vs University of Pennsylvania Smell Identification Test smell test for dupilumab)[27] were used in the studies, comparisons of objective tests are difficult, and a head-to-head study is required. Furthermore, safety results were similar between the placebo and mepolizumab treatment groups, as seen in previous nasal polyposis[15] and asthma studies.[16,28]

As an IL-5–specific antibody, mepolizumab selectively and effectively inhibits eosinophilic inflammation. In the majority of patients, nasal polyposis is characterized by local eosinophilic inflammation and high production of IL-5.[29,30] Expression of IL-5 and high levels of markers for T2 disease, such as IgE and eosinophil cationic protein, were also associated with an increased likelihood of asthma comorbidity.[22] In the mepolizumab group there was a 10-fold reduction in eosinophil counts at Week 25, which was accompanied by nasal polyp symptom improvements and reduced need for surgery. This reduction is consistent with results from the previous smaller study investigating mepolizumab in the treatment of nasal polyposis and studies investigating the use of mepolizumab in the treatment of severe eosinophilic asthma.[15,16,28] Although there was a reduction in eosinophil counts in the mepolizumab group, no improvements were seen in lung function outcomes. This is likely due to patients with asthma in this study having mild or moderate disease rather than severe eosinophilic asthma.

In the current study all patients were followed up 4 weeks after the final dose. Preliminary results from the discontinued follow-up stage suggested a sustained effect, but low patient numbers prevented conclusions from being made; similar results from the previous smaller mepolizumab study also suggested a sustained effect until 8 months after treatment in the responder subgroup.[15] Further research with higher numbers of patients is required to fully assess the duration of mepolizumab efficacy after treatment. Because nasal polyposis is not characterized by high production of IL-5 and eosinophilia in all patients[30] and not all patients respond to mepolizumab, additional future research should be designed to detect potential biomarkers that could be used to identify patients with nasal polyposis who are most likely to respond to mepolizumab treatment.[23] In this study with low patient numbers, *post hoc* analysis demonstrated that baseline blood eosinophil counts did not affect the responder rate and could not be used to identify responders.

One limitation of this study is the length of treatment. It is possible that efficacy could be increased with a longer treatment period because clinical improvements were continuing at the end of this 6-month study. For example, 2 patients were classified as responders for the first time at Week 25. Additionally, the time taken to recruit participants was longer than expected, given that only up to 4% of the population has nasal polyposis.[8] This issue will have to be noted and addressed for recruitment in future studies.

It should also be noted that in this study a dose of 750 mg of intravenous mepolizumab was administered every 4 weeks because this was the only dose available at the start of the study. As a result of more recent evidence,[16,31] a dose of 100 mg of mepolizumab subcutaneously every 4 weeks has been approved for the add-on maintenance treatment of adults with severe eosinophilic asthma[32] and will be used in future studies.

In conclusion, this study showed that mepolizumab significantly reduced the number of patients who met the criteria for needing surgery and improved nasal polyp scores and symptoms compared with placebo in patients with severe bilateral nasal polyposis treated with topical corticosteroids. Therefore mepolizumab treatment has the potential to improve the QoL of and reduce the surgery-associated burden for patients with nasal polyposis.

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Clinical implications: Results suggest that mepolizumab treatment has the potential to improve QoL and reduce surgery-associated burden for patients with severe nasal polyposis.

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METHODS

Study design and patients

The present study was a randomized, double-blind, placebo-controlled, multicenter study (NCT01362244). A randomization schedule was generated before the start of the study by using validated internal software. Patients were randomized with the GlaxoSmithKline IVRS system RAMOS. Site staff called the RAMOS system to register the patient on the system and allocated a randomization number. The randomization schedule used by the RAMOS system was generated by the GlaxoSmithKline study statistician before the start of the study using validated internal software. A center-based randomization schedule was used, with blocking (block size 4). The randomization was not stratified for any covariate. The patients and treating doctors were blind to treatment. A site third-party unblinded pharmacist dispensed the investigational product. Blinding was strictly maintained until all data had been collected and cleaned and Database Freeze had been declared, hence site staff (except for the unblinded pharmacist), GlaxoSmithKline study staff (except for the independent statistician who analyzed the interim data), and bioanalytical staff (placebo-treated subjects were not assayed for PK concentrations) had no access to the random codes until after completion of the study.

For inclusion, patients must have received a diagnosis of severe bilateral nasal polyps requiring surgery. Requirement for surgery was assessed by using an endoscopic nasal polyposis score of 3 or greater and a symptom score of greater than 7 on a VAS (Table E1). Patients were also required to be eligible for surgery, to have undergone at least 1 previous nasal polyp removal surgery, and to be considered refractory to steroids (still met the criteria for requiring surgery after continuous intranasal steroids for ≥3 months, received a short course of oral steroids, or both). Patients with concurrent asthma must be maintained on 10 mg/d or greater of oral corticosteroids (prednisolone or the equivalent). Additionally, they must not have had an asthma exacerbation requiring hospital admission within 4 weeks of screening. Treatment with immunotherapy within the previous 12 months also excluded patients from the study.

Patients had a 10- to 14-day run-in period with low-dose intranasal steroids before the first dose. This was required to prevent overtreatment with steroids and standardize treatment before study entry. Patients were instructed on administration of intranasal steroids, and daily administration was documented by using a diary card. At the end of the run-in period, patients were assessed for eligibility in the trial by using the criteria described in Table E1. Daily treatment with low-dose intranasal steroids continued throughout the study.

End points

Primary end point. The primary end point was a composite end point of the number of patients who no longer met the criteria for requiring surgery at the end of the treatment period (Week 25) based on assessment of nasal polyposis using the endoscopic nasal polyposis score and nasal polyposis severity VAS score (Table E2).

Secondary end points.

- The change in individual nasal polyposis VAS symptom scores was determined for the severity of 4 nasal polyposis symptoms (rhinorrhea, mucus in the throat, nasal blockage, and loss of smell). Subjects were asked to indicate on a VAS (0-10 cm) the severity of individual symptoms. Higher scores indicated more troublesome symptoms.
- Each nostril was assessed for polyps and graded to determine endoscopic nasal polyp scores.
- SNOT-22 questionnaires were completed. Patients were asked to rate the severity of their condition on each of 22 items by using a 0- to 5-point rating system. Higher scores indicated more severe symptoms.
- EQ-5D questionnaires were performed. The first part of the questionnaire assessed mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The second part asked the subjects to rate how good or bad their own health was that day on a scale of 0 to 100 (with a score of 100 being the best state of health).
- The following clinical pharmacodynamics assessments were performed: PnIF and lung function assessments (FEV_1, FVC, and PEFR).
- Olfaction tests were performed by using the Sniffin' Sticks Screening-12 to assess each subject's sense of smell. Each nostril was assessed separately.
- PK samples were obtained at time points outlined in the following assessments section. The predose PK sample could be taken at any point before dosing.
- The systemic exposure–clinical outcome relationship was determined, and anti-mepolizumab antibody testing was performed.

Safety end points. Safety end points were the monitoring of treatment-emergent AEs, vital signs, ECG results, and immunogenicity and clinical laboratory testing. The investigator or site staff were responsible for detecting, documenting, and reporting events that met the definition of an AE or serious AEs. Serious AEs were defined as any untoward medical occurrence that resulted in death, was life-threatening, required hospitalization, resulted in disability/incapacity, or was a congenital anomaly/birth defect.

Assessments

Assessments of endoscopic nasal polyposis scores, nasal polyposis severity VAS scores, individual VAS symptom scores, lung function, olfaction, nasal secretions, PnIF, pharmacodynamic blood samples, clinical tests, vital signs, ECGs, and AEs were performed on Weeks 1, 2, 5, 9, 13, 17, 21, and 25. SNOT-22 and EQ-5D questionnaires were performed on Weeks 1 and 25.

Safety monitoring occurred during intravenous infusion and for 1 hour at the end of infusion. Serious AEs/AEs, vital signs, and ECG results were assessed at each treatment visit (Weeks 1, 2, 5, 9, 13, 17, 21, and 25). Blood was taken for clinical laboratory tests and pharmacodynamics assessments at each treatment visit (Weeks 1, 2, 5, 9, 13, 17, 21, and 25). Immunogenicity was assessed at Weeks 1, 5, 13, and 25. PK was assessed at Weeks 1, 2, 5, 9, 13, and 25.

Analysis of individual-symptom VAS scores

Individual mean symptom scores were adjusted for baseline, visit, treatment group, and visit–treatment group interaction. The adjusted means are calculated by correcting the raw values to the overall mean baseline score of the 2 treatment groups using a statistical model. For example, if the baseline score for rhinorrhea was higher in the mepolizumab group than the placebo group, the Week 52 values would be adjusted according to the baseline mean of both groups. If the baseline scores were identical in both the mepolizumab and placebo groups, then the raw and adjusted means would be identical.

Box E1. List of investigators

Investigator	Subinvestigator	Description of research facility, hospital/institution, and address
Claus Bachert	Lien Calus, Els De Schryver, Lien Devuyst, Philippe Gevaert, Bauke Pauwels, Thibaut Van Zele	Upper Airways Research Laboratory, Ghent University, De Pintelaan 185, Ghent, 9000, Belgium
Wytske J. Fokkens	Gwijde Adriaensen, Marjolein E Cornet, Lim Keng Hua, Christine Segboer, Ingrid Terreehorst, Jochem Wigman	Academisch Medisch Centrum, Meibergdreef 9, Amsterdam, 1105 AZ, Netherlands
David Collier, Santdeep Paun (FPI), Ali Runa (FPI)	Jahangir Ahmed, C. Al Yaghchi, Moheimen Anwar	William Harvey Heart Centre, Clinical Research Centre, Charterhouse Square, London, EC1M 6BQ, United Kingdom
Stephen Durham	Moises Calderon	National Heart and Lung Institute, Dovehouse Street, London, SW3 6NP, United Kingdom
Valerie Lund	Harsha Kariyawasam, Rita Mirakian, Glenis Scadding, Yvonne Darby, Jo Rimmer, Simon Gane	Royal National Throat, Nose and Ear Hospital, 330 Grays Inn Road, London, WC1X 8DA, United Kingdom
Shuaib Nasser	None	Addenbrookes Hospital, Hills Road, Cambridge, CB2 2QQ, United Kingdom

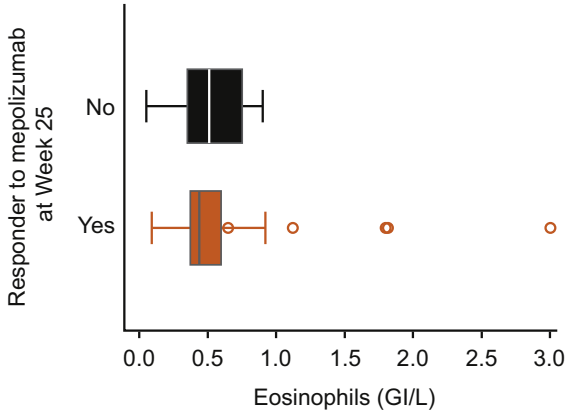

FIG E1. Patients in the mepolizumab group achieving a 1-point or greater improvement in total endoscopic nasal polyp score at Week 25 according to baseline eosinophil count (ITT population; *post hoc* analysis).

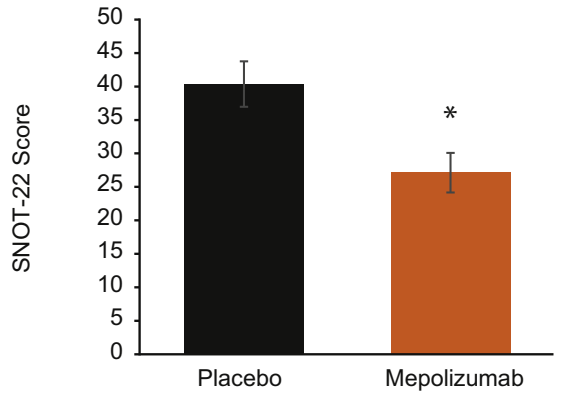

FIG E2. Adjusted means for SNOT-22 results at Week 25 (ITT population). Missing data are not imputed; *bars* represent SEs. *$P = .005$.

TABLE E1. Assessment of need for surgery (at screening/baseline)*

Nasal polyposis severity, VAS score	Is the subject eligible for entry into the treatment period? Endoscopic nasal polyp score			
	0	1	2	≥3
≤3	No	No	No	No
>3 to ≥7	No	No	No	No
>7	No	No	No	Yes

*Assessment parameters based on consensus of study investigators.

TABLE E2. Assessment of continuing need for surgery (primary end point)*

	Is the subject no longer in need of surgery?			
Nasal polyposis severity, VAS score	**Endoscopic nasal polyp score**			
	0	1	2	≥3
≤3	Yes	Yes	Yes	No
>3 to ≥7	Yes	Yes	Yes	No
>7	Yes	Yes	No	No

*Assessment parameters based on consensus of study investigators.

TABLE E3. Endoscopic nasal scoring criteria

Polyp score	Polyp size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle concha
2	Polyps reaching below the lower border of the middle turbinate
3	Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha
4	Large polyps causing almost complete congestion/obstruction of the inferior meatus

TABLE E4. Efficacy results for the composite primary end point and its individual components at Week 25 (ITT population)

Week 25	Placebo	Mepolizumab
Patients who no longer met the criteria for requiring polyposis surgery, n (%)*	n = 51, 5 (10)	n = 54, 16 (30)
Patients who still met the criteria for requiring polyposis surgery, n (%)	n = 51, 46 (90)	n = 54, 38 (70)
Worst affected endoscopic nasal polyp score, n (%)†	n = 31	n = 42
0	1 (3)	3 (7)
1	2 (6)	7 (17)
2	4 (13)	7 (17)
≥3	24 (77)	25 (60)
Improvement by ≥1 point in total endoscopic polyp score, n (%)†	n = 51, 14 (27)	n = 54, 27 (50)
Nasal polyposis severity VAS score, mean (95% CI)‡	n = 31, 6.1 (5.3-7.0)	n = 42, 4.3 (3.6-5.0)

Results are based on consensus between surgeons.
*Missing values were classified as nonresponders.
†*Post hoc* analysis.
‡VAS (0-10 cm) response to "How troublesome are your symptoms of nasal polyposis?": 0 = not troublesome, 10 = worst possible.

TABLE E5. Efficacy results for selected secondary end points at Week 25 (ITT population)

Week 25	Placebo, LS mean (95% CI)	Mepolizumab, LS mean (95% CI)	Treatment difference vs placebo (95% CI)	*P* value
Symptom severity, VAS score*	n = 31	n = 42		
Rhinorrhea	5.4 (4.5 to 6.2)	3.0 (2.3 to 3.8)	−2.3 (−3.4 to −1.2)	<.001
Mucus in throat	5.6 (4.8 to 6.4)	3.5 (2.8 to 4.2)	−2.1 (−3.2 to −1.0)	<.001
Nasal blockage	5.8 (5.0 to 6.6)	4.0 (3.3 to 4.8)	−1.8 (−2.9 to −0.7)	.002
Loss of smell	8.0 (7.2 to 8.7)	6.1 (5.4 to 6.8)	−1.9 (−2.9 to −0.9)	<.001
SNOT-22 score†	n = 32, 40.4 (33.6 to 47.1)	n = 42, 27.1 (21.2 to 33.0)	−13.2 (−22.2 to −4.2)	.005
EQ-5D Index score‡	n = 32	n = 41		
	0.91 (0.86 to 0.95)	0.91 (0.87 to 0.95)	0.00 (−0.06 to 0.07)	.891
EQ-5D VAS score§	n = 32	n = 42		
	75.5 (70.2 to 80.7)	81.1 (76.5 to 85.7)	5.7 (−1.3 to 12.7)	.111
PnIF	n = 32, 110.4 (92.9 to 127.8)	n = 42, 137.0 (121.2 to 152.9)	26.7 (3.1 to 50.2)	.027
Olfaction testing, mean of 2 nostrils‖	n = 32, 3.7 (2.8 to 4.6)	n = 41, 4.4 (3.6 to 5.2)	0.7 (−0.5 to 1.9)	.233
Lung function	n = 32	n = 42		
FEV_1 (L)	3.18 (3.05 to 3.32)	3.35 (3.23 to 3.47)	0.16 (−0.02 to 0.34)	.077
FVC (L)	4.41 (4.25 to 4.57)	4.59 (4.45 to 4.74)	0.18 (−0.03 to 0.40)	.094
PEFR (L/min)	467 (437 to 497)	481 (454 to 508)	14.1 (−25.8 to 54.0)	.484

LS, Least squares.

*VAS scale (0-10 cm; 0 = not troublesome, 10 = worst possible).

†SNOT-22 scores range from 0 to 110; lower scores imply less severe symptoms.

‡Weighted mean score of 5 questions; a score of 1 indicates full health, and lower scores indicate poorer health.

§VAS scale (0-100 mm; 0 = worst imaginable health state, 100 = best imaginable health state.)

‖Scores can range from 0 to 12, with lower scores indicating a worse sense of smell.

TABLE E6. Individual symptom VAS scores over the course of 25 weeks (ITT population)

	Week 1	Week 2	Week 5	Week 9	Week 13	Week 17	Week 21	Week 25
Rhinorrhea								
Treatment difference (95% CI)	0.05 (−0.90 to 1.01)	−0.86 (−1.82 to 0.10)	−1.15 (−2.11 to −0.18)	−1.94 (−2.93 to −0.95)	−1.59 (−2.62 to −0.55)	−2.35 (−3.40 to −1.29)	−1.83 (−2.91 to −0.75)	−2.31 (−3.41 to −1.21)
P value	.912	.078	.020	<.001	.003	<.001	.001	<.001
Mucus in throat								
Treatment difference (95% CI)	−0.25 (−1.22 to 0.72)	−0.47 (−1.44 to 0.51)	−0.52 (−1.50 to 0.45)	−2.11 (−3.11 to −1.11)	−1.29 (−2.33 to −0.25)	−2.04 (−3.10 to −0.98)	−1.58 (−2.66 to −0.50)	−2.09 (−3.19 to −1.00)
P value	.608	.347	.293	<.001	.015	<.001	.004	<.001
Nasal blockage								
Treatment difference (95% CI)	−0.11 (−1.07 to 0.85)	−0.93 (−1.89 to 0.03)	−1.03 (−2.00 to −0.06)	−1.67 (−2.66 to −0.68)	−1.31 (−2.35 to −0.28)	−1.36 (−2.42 to −0.29)	−1.31 (−2.39 to −0.23)	−1.77 (−2.87 to −0.67)
P value	.823	.057	.037	.001	.013	.012	.018	.002
Loss of smell								
Treatment difference (95% CI)	−0.04 (−0.94 to 0.87)	−0.23 (−1.13 to 0.68)	−0.45 (−1.36 to 0.46)	−1.19 (−2.13 to −0.26)	−1.26 (−2.23 to −0.29)	−1.32 (−2.31 to −0.33)	−1.40 (−2.41 to −0.39)	−1.88 (−2.91 to −0.85)
P value	.935	.625	.336	.012	.011	.009	.007	<.001

VAS scale (0-10 cm): 0 = not troublesome, 10 = worst possible (Treatment difference = Mepolizumab score − Placebo score).

TABLE E7. Mepolizumab versus placebo treatment differences in PD over the course of 25 weeks (ITT population)

	Week 2	Week 5	Week 9	Week 13	Week 17	Week 21	Week 25
PnIF (L/min)							
Treatment difference, mepolizumab vs placebo	21.16	16.89	7.20	27.71	15.40	29.51	26.65
SE	7.40	7.62	9.97	10.30	9.64	11.77	11.83
P value	.005	.029	.472	.009	.114	.014	.027
Olfaction score							
Treatment difference, mepolizumab vs placebo	0.09	1.14	0.79	0.73	0.38	0.65	0.71
SE	0.35	0.42	0.43	0.48	0.54	0.63	0.59
P value	.790	.008	.066	.127	.481	.308	.233
FEV_1 (L)							
Treatment difference, mepolizumab vs placebo	0.04	0.05	0.09	0.17	0.21	0.23	0.16
SE	0.07	0.08	0.10	0.09	0.11	0.10	0.09
P value	.567	.495	.365	.058	.056	.028	.077
FVC (L)							
Treatment difference, mepolizumab vs placebo	0.06	0.07	0.06	0.2	0.22	0.28	0.18
SE	0.08	0.08	0.10	0.10	0.12	0.11	0.11
P value	.486	.384	.546	.050	.061	.016	.094
PEFR (L/min)							
Treatment difference, mepolizumab vs placebo	5.11	14.55	8.91	23.24	38.16	38.72	14.13
SE	12.61	14.59	17.99	17.11	19.39	18.79	20.10
P value	.686	.321	.622	.178	.052	.042	.484

PD, Pharmacodynamics.

TABLE E8. Blood eosinophil counts over the course of 25 weeks (ITT population, *post hoc* analysis)

	Week 1	Week 2	Week 5	Week 9	Week 13	Week 17	Week 21	Week 25
Mepolizumab, n	53	54	54	53	45	45	42	54
Geometric mean, cells/μL (SD log)	500 (0.71)	80 (0.76)	40 (0.83)	40 (0.84)	30 (0.90)	30 (0.99)	30 (0.72)	50 (1.13)
Median ratio to baseline (minimum-maximum)	—	0.16 (0.0-1.2)	0.08 (0.0-1.2)	0.07 (0.0-0.8)	0.07 (0.0-3.1)	0.07 (0.0-0.8)	0.09 (0.0-1.0)	0.10 (0.0-1.3)
Placebo, n	51	51	49	48	41	35	34	45
Geometric mean, cells/μL (SD log)	470 (0.57)	450 (0.62)	450 (0.53)	450 (0.63)	450 (0.73)	380 (0.58)	390 (0.65)	380 (0.52)
Median ratio to baseline (minimum-maximum)	—	1.00 (0.5-1.5)	1.00 (0.6-2.1)	0.98 (0.5-2.4)	0.96 (0.1-3.0)	1.00 (0.4-1.8)	0.94 (0.4-2.4)	0.93 (0.4-1.8)

Geometric mean n values are presented.

TABLE E9. Final population PK model–derived summary parameters (ITT population)

Label	Estimate (SE)
Clearance (L/d)	0.22 (0.01)
Volume of distribution at SS (L)	7.10 (0.32)
Cmax (μg/mL)	193.22 (7.85)
Cmax (μg/mL) SS	268.40 (10.37)
AUC(0-inf [μg · d/mL])	3456.69 (152.11)
Cav(0-inf [μg/mL])	123.45 (5.43)
Half-life (α [d])	1.55 (0.41)
Half-life (β [d])	24.13 (1.03)

AUC, Area under curve; *Cmax*, maximum concentration; *SS*, steady state.

TABLE E10. AEs leading to treatment discontinuation

Age/sex	AE (preferred term)	Onset (study day)	Maximum intensity	Duration (d)	Outcome	Relation to study drug
Placebo						
46/M	Pneumonia/pneumonie	148	Moderate	58	Recovered/resolved	No
31/F	Eosinophilic pneumonia/eosinophilic pneumonia only left side	74	Moderate	201	Recovered/resolved	No
32/M	Cellulitis orbital/orbital (right) infection with cellulitis	56	Mild	27	Recovered/resolved	No
62/M	Lower respiratory tract infection/chest infection	160	Moderate	242	Recovered/resolved	No
43/M	Syncope patient fainted	28	Mild	0	Recovered/resolved	No
54/F	Anosmia/loss of sense of smell	1	Severe	89	Recovered/resolved	No
Mepolizumab						
53/F	Toxic skin eruption/rash, toxic eruption	31	Moderate	22	Recovered/resolved	Yes
63/M	Rash/rash	95	Severe	115	Recovered/resolved	Yes
NA/M	Hematuria/hematuria	NA	Mild	NA	Recovered/resolved	No
70/F	Hematuria/hematuria	55	Moderate	86	Recovered/resolved	No
Not assigned						
NA/M	Hematuria/hematuria	NA	NA	NA	Recovered/resolved	No

F, Female; *M*, male; *NA*, not available.