

# Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial

Joseph K Han, Claus Bachert, Wytse Fokkens, Martin Desrosiers, Martin Wagenmann, Stella E Lee, Steven G Smith, Neil Martin, Bhabita Mayer, Steven W Yancey, Ana R Sousa, Robert Chan, Claire Hopkins, on behalf of the SYNAPSE study investigators\*



## Summary

**Background** Chronic rhinosinusitis with nasal polyps affects approximately 2–4% of the general population, and long-term use of systemic corticosteroids is associated with adverse effects. The aim of this study was to assess the efficacy and safety of mepolizumab in adults with recurrent, refractory severe bilateral chronic rhinosinusitis with nasal polyps.

**Methods** SYNAPSE was a randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial done at 93 centres, mainly hospitals, in 11 countries. Eligible patients were aged 18 years or older with recurrent, refractory, severe, bilateral nasal polyp symptoms (nasal obstruction symptom visual analogue scale [VAS] score of >5), were eligible for repeat nasal surgery (overall symptoms VAS score >7 and endoscopic nasal polyps score of ≥5, with a minimum score of 2 in each nasal cavity) despite standard of care treatment, and had to have at least one nasal surgery in the past 10 years. Patients were randomly assigned (1:1), using permuted block design, to receive either 100 mg mepolizumab subcutaneously or placebo once every 4 weeks, in addition to standard of care (mometasone furoate intranasal spray for at least 8 weeks before screening and during the study, saline nasal irrigations, systemic corticosteroids or antibiotics, or both), as required, for 52 weeks. Site staff, the central study team, and patients were masked to study treatment and absolute blood eosinophil counts. The coprimary endpoints were change from baseline in total endoscopic nasal polyp score at week 52 and in mean nasal obstruction VAS score during weeks 49–52, assessed in the intention-to-treat population (ITT). This study is registered with ClinicalTrials.gov, NCT03085797.

**Findings** From May 25, 2017, to Dec 12, 2018, 854 patients were screened for eligibility. 414 patients were randomly assigned with 407 included in the ITT population; 206 received mepolizumab and 201 received placebo. Total endoscopic nasal polyp score significantly improved at week 52 from baseline with mepolizumab versus placebo (adjusted difference in medians  $-0.73$ , 95% CI  $-1.11$  to  $-0.34$ ;  $p < 0.0001$ ) and nasal obstruction VAS score during weeks 49–52 also significantly improved ( $-3.14$ ,  $-4.09$  to  $-2.18$ ;  $p < 0.0001$ ). Adverse events considered related to study treatment were reported in 30 (15%) of 206 patients receiving mepolizumab and 19 (9%) of 201 receiving placebo. On-treatment serious adverse events occurred in 12 (6%) patients receiving mepolizumab and 13 (6%) receiving placebo; none were considered related to treatment in those receiving mepolizumab. One death was reported in the placebo group (myocardial infarction; death occurred 99 days after the last dose) and was considered unrelated to the treatment.

**Interpretation** Mepolizumab treatment improved nasal polyp size and nasal obstruction compared with placebo, with no new safety indications, in patients with recurrent, refractory severe chronic rhinosinusitis with nasal polyps. These findings suggest that mepolizumab provides an effective add-on treatment option to standard of care in this population.

**Funding** GlaxoSmithKline.

**Copyright** © 2021 Elsevier Ltd. All rights reserved.

## Introduction

Chronic rhinosinusitis with nasal polyps is a subtype of chronic rhinosinusitis affecting approximately 2–4% of the general population.<sup>1,2</sup> It is characterised by chronic local eosinophilic inflammation, often type 2 (T2) inflammation, with interleukin (IL)-5 playing a key pathogenic role.<sup>3–6</sup> Symptoms of this disease include nasal blockage, loss of smell, facial pressure, and rhinorrhoea, which can have a substantial impact on health-related quality of life.<sup>7–9</sup>

Current standard of care includes intranasal corticosteroids, short courses of systemic corticosteroids, and nasal surgery.<sup>2</sup> Although systemic corticosteroids reduce the inflammatory response and might temporarily reduce nasal polyp size and improve symptoms, their long-term use is associated with adverse effects.<sup>2,10</sup> Furthermore, surgery is associated with high recurrence rates, and scarring or mucosal damage, or both.<sup>11,12</sup> Patients also express concerns about the risks associated with surgery, including general anaesthesia and discomfort.<sup>13,14</sup> As such,

*Lancet Respir Med* 2021;  
9: 1141–53

Published Online  
April 16, 2021  
[https://doi.org/10.1016/S2213-2600\(21\)00097-7](https://doi.org/10.1016/S2213-2600(21)00097-7)  
See [Comment](#) page 1081

\*Members listed in appendix

Department of Otolaryngology, Eastern Virginia Medical School, Norfolk, VA, USA (J K Han MD); Department of Oto-Rhino-Laryngology, Upper Airways Research Laboratory, Ghent University Hospital, Ghent University, Ghent, Belgium (Prof C Bachert PhD); Division of ENT Diseases, CLINTEC, Karolinska Institutet, University of Stockholm, Stockholm, Sweden (Prof C Bachert); Department of Otolaryngology, Amsterdam University Medical Center, Amsterdam, Netherlands (Prof W Fokkens PhD); Division of Otolaryngology-Head and Neck Surgery, Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada (Prof M Desrosiers MD); Department of Otorhinolaryngology, HNO-Klinik, Universitätsklinikum Düsseldorf, Düsseldorf, Germany (Prof M Wagenmann MD); Department of Otolaryngology-Head and Neck Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA (S E Lee MD); Respiratory Therapeutic Area Unit, GlaxoSmithKline, Research Triangle Park, NC, USA (S G Smith PhD, S W Yancey MSc); GlaxoSmithKline, London, UK (N Martin MD, B Mayer MSc, A R Sousa PhD, R Chan MD); Department of ENT, Guy's Hospital, London, UK (Prof C Hopkins DM); St Thomas' Hospital, King's College London, London, UK (Prof C Hopkins)

Correspondence to:  
Dr Joseph K Han, Department of  
Otolaryngology, Eastern Virginia  
Medical School, Norfolk,  
VA 23507, USA  
[hanjk@evms.edu](mailto:hanjk@evms.edu)

See Online for appendix

## Research in context

### Evidence before this study

Patients with severe chronic rhinosinusitis with nasal polyps often require nasal surgery, and those with eosinophil-rich nasal polyps have a higher postoperative recurrence rate. As such, anti-interleukin (IL)-5 therapies might be an effective treatment option for these patients. Mepolizumab can reduce eosinophilic inflammation in severe eosinophilic asthma, eosinophilic granulomatosis with polyangiitis, and hypereosinophilic syndrome. We searched PubMed for studies of mepolizumab in nasal polyps published in English from database inception to Sept 15, 2020. The search identified two publications describing the efficacy of 750 mg mepolizumab administered intravenously at 4-week intervals in two phase 2, randomised, clinical trials. In the first trial, mepolizumab treatment reduced nasal polyp size at week 8 after two doses, compared with placebo. In the second trial, patients received six doses of mepolizumab over 24 weeks, which reduced the need for surgery, and improved nasal polyp symptoms and health-related quality of life, compared with placebo. In both studies, the safety profile of mepolizumab was similar to that of placebo. We did not identify any trials of mepolizumab at 100 mg administered subcutaneously (approved in severe eosinophilic asthma) for nasal polyps. An additional search for phase 3 trials of biological therapies in patients with severe uncontrolled chronic rhinosinusitis with nasal polyps identified two studies in which the IL-4 and IL-13 inhibitor dupilumab reduced nasal polyp size, sinus disease burden, and symptom severity; improved sense of smell and health-related quality of life; and reduced the use of systemic corticosteroids and the need for nasal polyp surgery in these

patients. In addition, two phase 3 studies were identified in which the anti-IgE antibody omalizumab reduced nasal polyp size and improved symptoms in patients with severe chronic rhinosinusitis with nasal polyps who had an inadequate response to intranasal corticosteroids.

### Added value of this study

To our knowledge, this is the first large, multinational, phase 3 study to show the safety and efficacy of an anti-IL-5 biologic in patients with recurrent, refractory, severe chronic rhinosinusitis with nasal polyps, despite continuous medical treatment and previous surgical treatment, who were eligible for repeat nasal surgery. We showed that mepolizumab improved nasal polyp size and nasal obstruction, reduced need for actual nasal surgery and systemic corticosteroid use, and improved sinonasal symptoms and health-related quality of life with an acceptable safety profile. Our findings are consistent with, and build on, those from previous mepolizumab studies, and further increase understanding of the effect that mepolizumab has on symptoms, surgery, and corticosteroid use in this population with a high symptom burden and refractory disease.

### Implications of all the available evidence

Evidence to date suggests that mepolizumab treatment reduces nasal polyp size and improves associated symptoms and reduces the need for actual surgery and systemic corticosteroid use in patients with chronic rhinosinusitis with nasal polyps. Given that these are key goals of nasal polyp management, mepolizumab provides an effective add-on treatment option to standard care for patients with chronic rhinosinusitis with nasal polyps.

novel therapies targeting cytokines involved in T2 inflammation associated with chronic rhinosinusitis with nasal polyps, such as IL-5, are required.

Mepolizumab is a humanised monoclonal antibody that selectively binds to and inactivates IL-5, thereby inhibiting eosinophilic inflammation.<sup>15</sup> Mepolizumab at 100 mg administered subcutaneously is approved in multiple countries for patients 6 years or older with severe eosinophilic asthma, and at a dose of 300 mg for adults with eosinophilic granulomatosis with polyangiitis or hypereosinophilic syndrome in the USA.<sup>16,17</sup>

Previous studies<sup>18,19</sup> have shown reductions in polyp size, improved symptoms, and a reduced need for nasal surgery in patients with chronic rhinosinusitis with nasal polyps receiving 750 mg of intravenous mepolizumab. The aim of this phase 3 study was to assess the efficacy and safety of mepolizumab at a dose of 100 mg administered subcutaneously for 52 weeks, compared with placebo (both treatments were added to standard of care, which included use of systemic corticosteroids), in adults with recurrent, refractory, severe, bilateral chronic rhinosinusitis with nasal polyps who were eligible for repeat surgery.

## Methods

### Study design and participants

SYNAPSE was a randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial done at 93 centres, mainly hospitals, in 11 countries (Argentina, Australia, Canada, Germany, the Netherlands, South Korea, Romania, Russia, Sweden, the UK, and the USA).

Eligible patients were aged 18 years or older with recurrent, refractory, severe, bilateral nasal polyp symptoms (nasal obstruction symptom visual analogue scale [VAS] score of >5 [maximum 10]) and were eligible for repeat nasal surgery (overall symptoms VAS score >7 and endoscopic nasal polyps score of ≥5 [maximum 8], with a minimum score of 2 in each nasal cavity), despite standard of care treatment. Patients had to have at least one nasal surgery (defined as any incision [cutting open] of the paranasal sinuses and removal of polyp tissue from the nasal cavity [polypectomy] and the sinuses) in the past 10 years. In addition, patients required stable maintenance therapy with intranasal spray medication (mometasone furoate) for at least 8 weeks before screening, and displayed two or more different symptoms for at least 12 weeks before screening (nasal

blockage, obstruction, and congestion, or nasal discharge [anterior or posterior nasal drip]), with one or more of the following symptoms: nasal discharge, facial pain or pressure, and reduction or loss of smell. Full inclusion and exclusion criteria are provided in the appendix (p 3).

The trial was done in accordance with ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines from the International Conference on Harmonisation, and any applicable country-specific regulatory requirements. All patients provided written informed consent before study initiation. The study was approved by local ethics review boards at the participating sites. The protocol is available at <https://www.gsk-studyregister.com/>.<sup>20</sup>

### Randomisation and masking

Patients were randomly assigned (1:1) to receive either mepolizumab or placebo once every 4 weeks, in addition to standard of care for 52 weeks. Randomisation was done using an interactive response system. The randomisation sequence was computer generated by sponsor validated software (RandALL NG; version 1.3.3), done separately for each country, using permuted block design of block size 6. The allocation sequence was computer generated and investigators were informed of patients' treatment assignment via an interactive response technology system. Mepolizumab and placebo were identical in appearance. Site staff, the central study team, and patients were masked to study treatment and absolute blood eosinophil counts (including white blood cell differentials); masking was maintained for the duration of the trial.

### Procedures

Following a 4-week run-in period, patients received mepolizumab at 100 mg subcutaneously or placebo once every 4 weeks (using a safety syringe), in addition to standard of care for 52 weeks (appendix p 9). In line with the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020,<sup>2</sup> standard of care consisted of daily mometasone furoate intranasal spray throughout the study period, in addition to saline nasal irrigations, and courses of systemic corticosteroids or antibiotics, or both, as required. Patients were placed on the maximum dose of mometasone furoate spray (two doses of 50 µg into each nostril twice a day) or in line with the local standard dose and frequency at the start of the run-in period. Patients who had nasal surgery or received systemic corticosteroids during the study could continue study treatment until the end of the 52-week treatment period. Patients prematurely discontinuing study treatment could still attend study visits for off-treatment assessments. The study was designed to follow up to the first 200 randomly assigned patients for 6 months after stopping treatment. Recruitment of patients was halted so that the follow-up period did not extend beyond the projected last visit for the last randomly assigned patient.

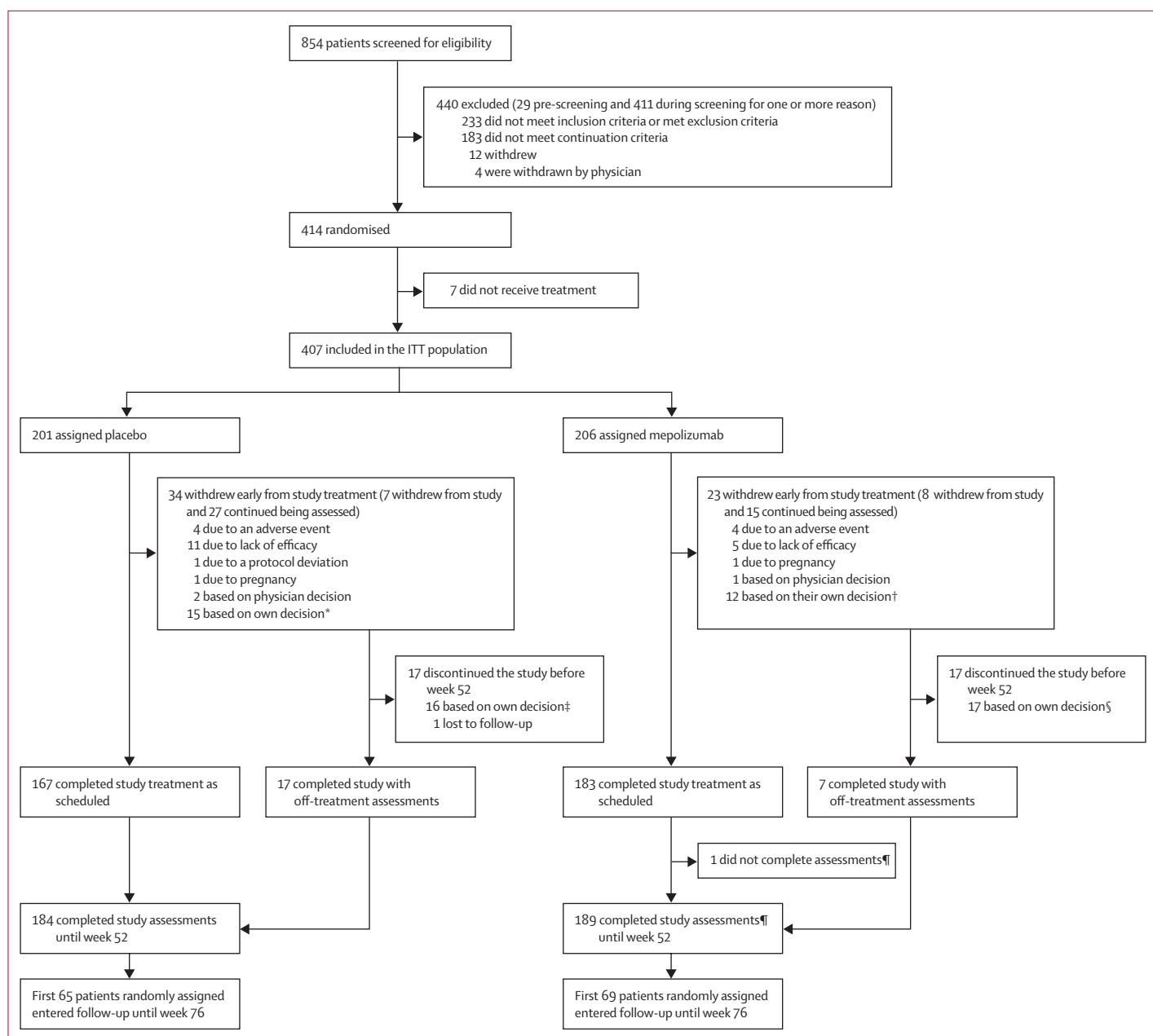
Endoscopic nasal polyp score was assessed at each study visit by trained health-care staff and images of endoscopies were sent to central laboratories for scoring by independent masked reviewers. During the 4-week run-in period and the treatment period, patients recorded symptoms (nasal obstruction, nasal discharge, throat mucus, loss of smell, facial pain, and overall symptom VAS scores) daily in an eDiary using a VAS scale (0–100); scores were divided by 10 and reported across a range from 0·0 (none) to 10·0 (as bad as you can imagine), according to their current state.

The 22-item Sino-Nasal Outcome Test (SNOT-22), a disease-specific measure of health-related quality of life, was completed by patients at each study visit every 4 weeks. Peak nasal inspiratory flow was assessed at each study visit, with the highest value taken from three consecutive readings. University of Pennsylvania Smell Identification Test (UPSIT) was assessed at baseline and then on alternating visits (every 8 weeks) but was carried out only in three countries (Canada, the UK, and the USA). Blood samples for haematology were taken at each study visit. Safety (review of adverse events and serious adverse events) and vital signs were assessed at each study visit. A 12-lead ECG, blood samples for immunogenicity, and other laboratory assessments (eg, liver chemistries) were carried out at baseline and at week 52.

### Outcomes

The coprimary endpoints were change from baseline in total endoscopic nasal polyp score at week 52 and in mean nasal obstruction VAS score during weeks 49–52. Total endoscopic nasal polyp score was the sum of left and right nostril scores ranging from 0 (no polyps) to 4 (large polyps causing complete obstruction of the inferior meatus) for each nostril, giving a total score of up to 8. The VAS score could range from 0·0 to 10·0, as used in previous studies of nasal polyps.<sup>19,21–23</sup> The key secondary endpoint was time-to-first nasal surgery until week 52. Other secondary endpoints were the proportion of patients requiring systemic corticosteroids for nasal polyps until week 52 and change from baseline in: mean overall VAS symptom score during weeks 49–52, SNOT-22 total score at week 52, mean composite VAS score (combining scores for nasal obstruction, nasal discharge, throat mucus, and loss of smell) during weeks 49–52, and mean VAS score for loss of smell during weeks 49–52. SNOT-22 scores ranged from 0 to 110, and have a minimal clinically important difference of 8·9 units.<sup>24</sup> Primary and secondary efficacy endpoints were assessed in the intention-to-treat (ITT) population, defined as all randomly assigned patients who received at least one dose of the study drug, analysed according to the allocated treatment.

Other exploratory endpoints included: the proportion of patients with a decrease of 1 or more points from



**Figure 1: Trial profile**

Patients could have had more than one reason for being excluded during screening. ITT=intention-to-treat. \*Burden of procedures (n=2), patient relocated (n=1), and other (n=13). One patient selected two reasons for withdrawal: burden of procedures and other. †Frequency of visits (n=1), patient relocated (n=2), burden of procedures (n=2), and other (n=7). ‡Frequency of visits (n=2), patient relocated (n=1), and other (n=13). §Patient relocated (n=2), burden of procedures (n=2), other (n=12), and no reason reported (n=1). ¶This patient completed the study treatment as scheduled, but withdrew from the study before week 52.

baseline in nasal polyps score at week 52 in the absence of surgery; number of courses of systemic corticosteroids; antibiotics up to week 52; the proportion of patients with a decrease of 8.9 points or more from baseline in SNOT-22 total score in the absence of surgery;<sup>24</sup> the proportion of patients no longer needing surgery (defined as an overall symptom VAS score of  $\leq 7$  during weeks 49–52, a total endoscopic score of  $< 5$  at week 52,

and no nasal surgery during the treatment period); change from baseline in UPSIT (maximum score 40); and on-treatment blood eosinophil count. Additional pre-specified analyses (outside of the original analysis plan) were change from baseline in: loss of smell VAS score by the number of previous surgeries (one, two, or more than two) at week 49–52 and peak nasal inspiratory flow at week 52. Post-hoc analyses

	Placebo (n=201)	Mepolizumab (n=206)
Age, years	48.9 (12.5)	48.6 (13.6)
Female	76 (38%)	67 (33%)
Male	125 (62%)	139 (67%)
Race		
White and European	183 (91%)	190 (92%)
East Asian	7 (3%)	6 (3%)
Black and African American	4 (2%)	5 (2%)
Arabic and North African	4 (2%)	2 (1%)
Central and South Asian	1 (1%)	2 (1%)
South East Asian	1 (1%)	1 (1%)
Multiple	1 (1%)	0
Ethnicity		
Hispanic or Latino	29 (14%)	24 (12%)
Not Hispanic and not Latino	172 (86%)	182 (88%)
Body-mass index, kg/m <sup>2</sup>		
Median	27.2 (24.6–30.5)	27.4 (24.4–30.3)
Mean	28.2 (5.5)	28.2 (5.3)
Duration of nasal polyps, years		
Median	10.0 (5.3–16.0)	9.0 (5.0–15.3)
Mean	11.5 (8.3)	11.4 (8.5)
Previous nasal surgery		
0	0	0
≥1	201 (100%)	206 (100%)
≥2	120 (60%)	98 (48%)
≥3	73 (36%)	51 (25%)
≥4	38 (19%)	24 (12%)
≥5	26 (13%)	11 (5%)
Time since previous nasal polyp surgery, years*		
Median	3.0 (1.7–5.6)	3.8 (1.9–6.2)
Mean	3.8 (2.7)	4.2 (2.7)
Systemic corticosteroid courses for nasal polyps in the past 12 months		
0	110 (55%)	100 (49%)
≥1	91 (45%)	106 (51%)
≥2	44 (22%)	42 (20%)

(Table 1 continues in next column)

	Placebo (n=201)	Mepolizumab (n=206)
(Continued from previous column)		
Total endoscopic score (scale 0–8)		
Median	6.0 (5.0–6.0)	5.0 (5.0–6.0)
Mean	5.6 (1.4)	5.4 (1.2)
Nasal obstruction VAS score (scale 0–10)†		
Median	9.1 (8.5–9.7)	9.0 (8.3–9.6)
Mean	9.0 (0.8)	8.9 (0.8)
Overall symptom VAS score (scale 0–10)†		
Median	9.2 (8.7–9.8)	9.1 (8.4–9.7)
Mean	9.1 (0.7)	9.0 (0.8)
Nasal symptom composite‡ score (scale 0–10)†		
Median	9.2 (8.6–9.6)	9.1 (8.5–9.6)
Mean	9.0 (0.8)	9.0 (0.8)
Loss of smell VAS score (scale 0–10)†		
Median	10.0 (9.6–10.0)	10.0 (9.6–10.0)
Mean	9.7 (0.6)	9.6 (0.8)
SNOT-22 total score†		
Median	64.0 (51.0–77.0)	64.0 (50.0–77.0)
Mean	64.4 (19.0)	63.7 (17.6)
Patients with asthma	149 (74%)	140 (68%)
Patients with aspirin-exacerbated respiratory disease	63 (31%)	45 (22%)
Blood eosinophil count, cells per µL§	400 (0.91)	390 (0.88)

Data are n (%), mean (SD), or median (IQR). SNOT=Sino-Nasal Outcome Test. VAS=visual analogue scale. \*Includes patients with partial dates for previous surgery; if day was missing, assumed as the last day of the month; if month was missing, assumed as December. †Higher scores indicate greater disease severity or worse quality of life. ‡Combining scores for nasal obstruction, nasal discharge, throat mucus, and loss of smell. §Geometric mean (coefficient of variation).

**Table 1: Baseline demographics and patient characteristics (ITT population)**

### Statistical analysis

The study was designed to continue to collect data for patients who prematurely discontinued treatment; all data reported up to week 52 were included in the analysis, regardless of treatment discontinuation. A sample size of 400 patients was estimated to provide more than 90% power to detect a statistical significance (at two-sided significance of 0.05) for coprimary endpoints and the key secondary endpoint. For coprimary endpoints, the true effect size used in the power calculation was based on results observed in the previous 6-month phase 2 trial<sup>19</sup> of mepolizumab in patients with chronic rhinosinusitis with nasal polyps, in which 52% patients receiving mepolizumab (*vs* 27% receiving placebo) had an improvement in nasal polyp score of 1-point or more and 70% (*vs* 39%) had an improvement in nasal obstruction VAS score of 1-point or more. In the phase 2 trial,<sup>19</sup> 20% of patients receiving placebo had surgery; the sample size was based on a true reduction in the proportion of patients receiving surgery until week 52 from 40% (placebo group) to 25% (mepolizumab group).

were the exacerbation rates and Asthma Control Questionnaire-5 scores at week 52 in patients with comorbid asthma.

Safety assessments included monitoring for adverse events, serious adverse events, local injection site reactions, and systemic reactions; clinically significant changes in haematological and clinical chemistry; and 12-lead ECG and immunogenicity. Safety was assessed in the safety population, defined as all randomly assigned patients who received at least one dose of the study drug, analysed according to the treatment received. Adverse events and serious adverse events were coded per the Medical Dictionary for Regulatory Activities (V22.1). Mepolizumab plasma concentrations were assessed at week 4 and 52 before dosing (data not shown).



	Placebo (n=201)			Mepolizumab (n=206)			Treatment effect (95% CI); p value
	Median change from baseline	Mean (SD) change from baseline	Proportion of patients, n (%)	Median change from baseline	Mean (SD) change from baseline	Proportion of patients, n (%)	
Coprimary endpoints							
Change from baseline in total endoscopic nasal polyp score at week 52*	0.00	-0.1 (1.46)	..	-1.00	-0.9 (1.90)	..	-0.73 (-1.11 to -0.34)†; p<0.0001‡
Change from baseline in nasal obstruction VAS score during weeks 49–52*	-0.82	-2.5 (3.15)	..	-4.41	-4.2 (3.42)	..	-3.14 (-4.09 to -2.18)†; p<0.0001‡
Secondary endpoints							
Proportion of patients having nasal surgery up to week 52 (time-to-first nasal surgery)	..	..	46 (23%)	..	..	18 (9%)	0.43 (0.25 to 0.76)§; p=0.0032
Change from baseline in overall symptom VAS score during weeks 49–52*	-0.90	-2.5 (3.08)	..	-4.48	-4.3 (3.43)	..	-3.18 (-4.10 to -2.26)†; p=0.0032‡
Change from baseline in SNOT-22 total score at week 52*	-14.00	-15.7 (23.93)	..	-30.00	-29.4 (24.67)	..	-16.49 (-23.57 to -9.42)†; p=0.0032‡
Proportion of patients requiring systemic corticosteroids (≥1 course) for nasal polyps until week 52	..	..	74 (37%)	..	..	52 (25%)	0.58 (0.36 to 0.92)¶; p=0.020
Change from baseline in composite** VAS score during weeks 49–52*	-0.89	-2.2 (2.82)	..	-3.96	-3.8 (3.19)	..	-2.68 (-3.44 to -1.91)†; p=0.020‡
Change from baseline in loss of smell VAS symptom score during weeks 49–52*	0.00	-1.4 (2.65)	..	-0.53	-2.8 (3.61)	..	-0.37 (-0.65 to -0.08)†; p=0.020‡
Data are median, mean (SD), and n (%), unless stated otherwise. SNOT=Sino-Nasal Outcomes Test. VAS=visual analogue scale. *Patients who required nasal surgery before the visit or time period were assigned their worst observed score recorded before surgery; patients with no nasal surgery who withdrew before the visit or time period were assigned their worst observed score before study withdrawal; patients with missing data were assigned their worst observed score before the missing visit. †Adjusted difference in medians; quantile regression with covariates of treatment group, geographic region, baseline score, and log, baseline blood eosinophil count. ‡p value based on Wilcoxon rank-sum test. Adjusted p values for secondary endpoints, multiplicity controlled using a closed testing procedure according to a predefined hierarchy of testing. §Hazard ratio (95% CI); Cox proportional hazards model with covariates of treatment group, baseline nasal polyp score, baseline nasal obstruction score, log, baseline blood eosinophil count, number of previous surgeries (one, two, or more than two; ordinal), and geographic region. ¶Odds ratio (95% CI); logistic regression model with covariates of treatment group, baseline nasal polyp score, baseline nasal obstruction score, log, baseline blood eosinophil count, number of systemic corticosteroid courses in previous 12 months (0, 1, >1; ordinal), and geographic region. **Combining scores for nasal obstruction, nasal discharge, throat mucus, and loss of smell.							
Table 2: Summary of efficacy outcomes							

Following testing of coprimary endpoints, multiplicity arising from multiple secondary endpoints was controlled using a closed testing procedure according to a predefined hierarchy of secondary endpoints: time-to-first nasal surgery, overall symptom VAS score, SNOT-22 total score, systemic corticosteroids for nasal polyps use, composite VAS score, and loss of smell VAS score. Both coprimary endpoints had to be statistically significant to continue testing to the secondary endpoints. Statistical significance was only possible for each secondary endpoint in the hierarchy if the previous endpoint was significant.

Occurrence of nasal surgery at any time following randomisation was an anticipated intercurrent event (ie, expected to affect evaluation of subsequent scores) for the coprimary and symptom and health-related quality of life-based secondary endpoints. Patients who underwent nasal surgery before week 52 were assigned their worst observed score, recorded before the surgery, for all subsequent visits. Further details on estimands for the coprimary and key secondary endpoints are provided in the appendix (p 6). Patients who withdrew early from the study without having undergone nasal surgery or who had missing data for any other reason were assigned their worst observed score, recorded before study withdrawal or the missing visit. A sensitivity

analysis, for patients who underwent nasal surgery up to week 52 or withdrew early from the study and were assigned the worst possible score for all subsequent visits, was also carried out (appendix p 6). Use of systemic corticosteroids during the treatment period was considered part of standard of care; therefore, observed scores following systemic corticosteroids use were included in the analyses.

For coprimary endpoints, VAS scores, SNOT-22 score, peak nasal inspiratory flow, and UPSIT, the non-parametric Wilcoxon rank-sum test was used to assess the difference in change from baseline scores between treatment groups; estimates of the treatment effect accounting for covariates of treatment group, geographical region (country for UPSIT analysis), baseline score, and log<sub>e</sub> baseline blood eosinophil count were presented as a difference in medians between treatment groups based on a quantile regression model using the bootstrap approach with 1000 000 replicates.<sup>25,26</sup>

Time-to-nasal surgery was analysed using a Cox proportional hazards model with covariates of treatment group, baseline nasal polyp score (centrally read), baseline nasal obstruction VAS score, log<sub>e</sub> baseline blood eosinophil count, number of previous surgeries (one, two, or more than two; ordinal), and geographical region. The proportion of patients requiring systemic

corticosteroids for nasal polyps was analysed using a logistic regression model with covariates of treatment group, baseline nasal polyp score (centrally read), baseline nasal obstruction VAS score, log<sub>e</sub> baseline blood eosinophil count, number of systemic corticosteroids courses in previous 12 months (none, one, or more than one; ordinal), and geographic region. Blood eosinophil counts were log transformed and analysed using mixed model repeated measures with covariates of treatment group, geographical region, visit, and baseline log<sub>e</sub> blood eosinophil count, plus interaction terms for visit by baseline and visit by treatment group.

For the coprimary endpoints, the treatment effect was presented as difference in medians to reduce the influence of extremes in the data. A post-hoc analysis was carried out using a mixed model for repeated measures with estimates of the treatment effect presented as a difference in means (appendix p 6). All data were analysed using SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT03085797 (GlaxoSmithKline ID: 205687).

### Role of the funding source

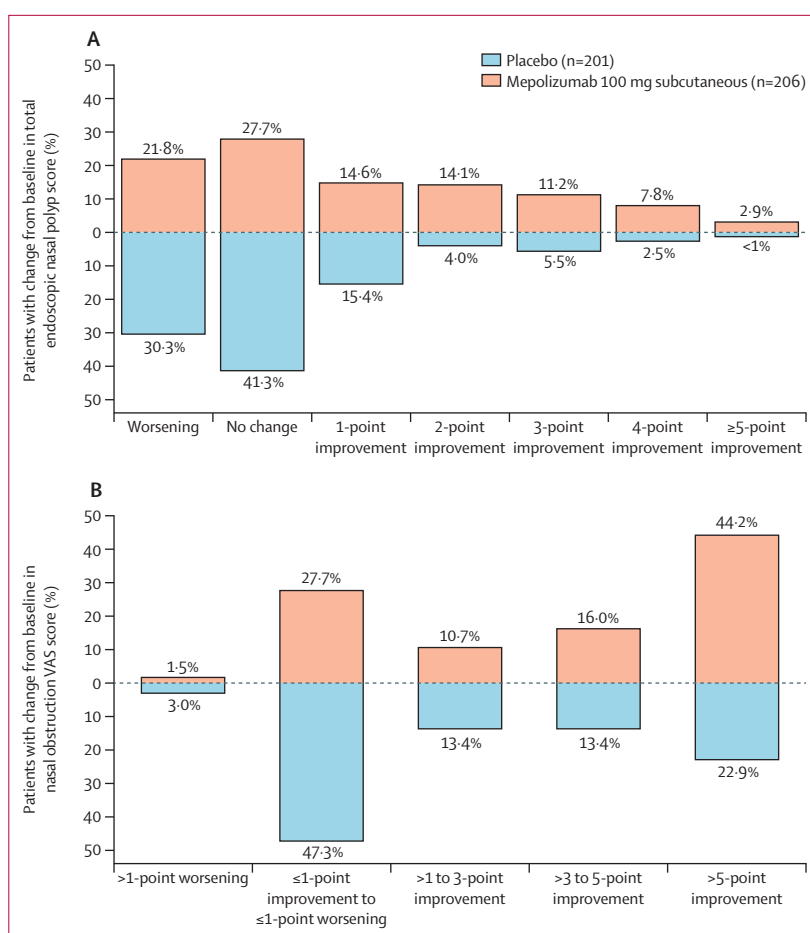
The funder of the study funded the medical writing and editorial support (in the form of writing assistance, including preparation of the draft manuscript under direction and guidance of the authors, collating and incorporating authors' comments for each draft, assembling tables and figures, grammatical editing and referencing). The sponsor did not place any restrictions on access to the data or on the statements made in the manuscript.

## Results

From May 25, 2017, to Dec 12, 2018, 854 patients were screened for eligibility. Overall, 414 patients were randomly assigned with 407 included in the ITT population; 206 received mepolizumab and 201 received placebo (figure 1). 15 patients (eight [4%] of 206 receiving mepolizumab and seven [3%] of 201 receiving placebo) discontinued treatment and withdrew from the study before week 52; 42 patients (15 [7%] receiving mepolizumab and 27 [13%] receiving placebo) discontinued treatment and continued being assessed.

Patient demographics and baseline characteristics were similar between treatment groups, and most patients were white (373 [92%] of 407) and male (264 [65%]). The mean age was 48.8 years (SD 13.01), and mean body-mass index was 28.2 kg/m<sup>2</sup> (5.4). However, a lower proportion of patients in the mepolizumab versus placebo group had two or more previous nasal surgeries and aspirin-exacerbated respiratory disease (AERD), and patients in the mepolizumab group had lower total endoscopic nasal polyps scores at baseline (table 1).

For the coprimary endpoints, total endoscopic nasal polyp score significantly improved at week 52 from

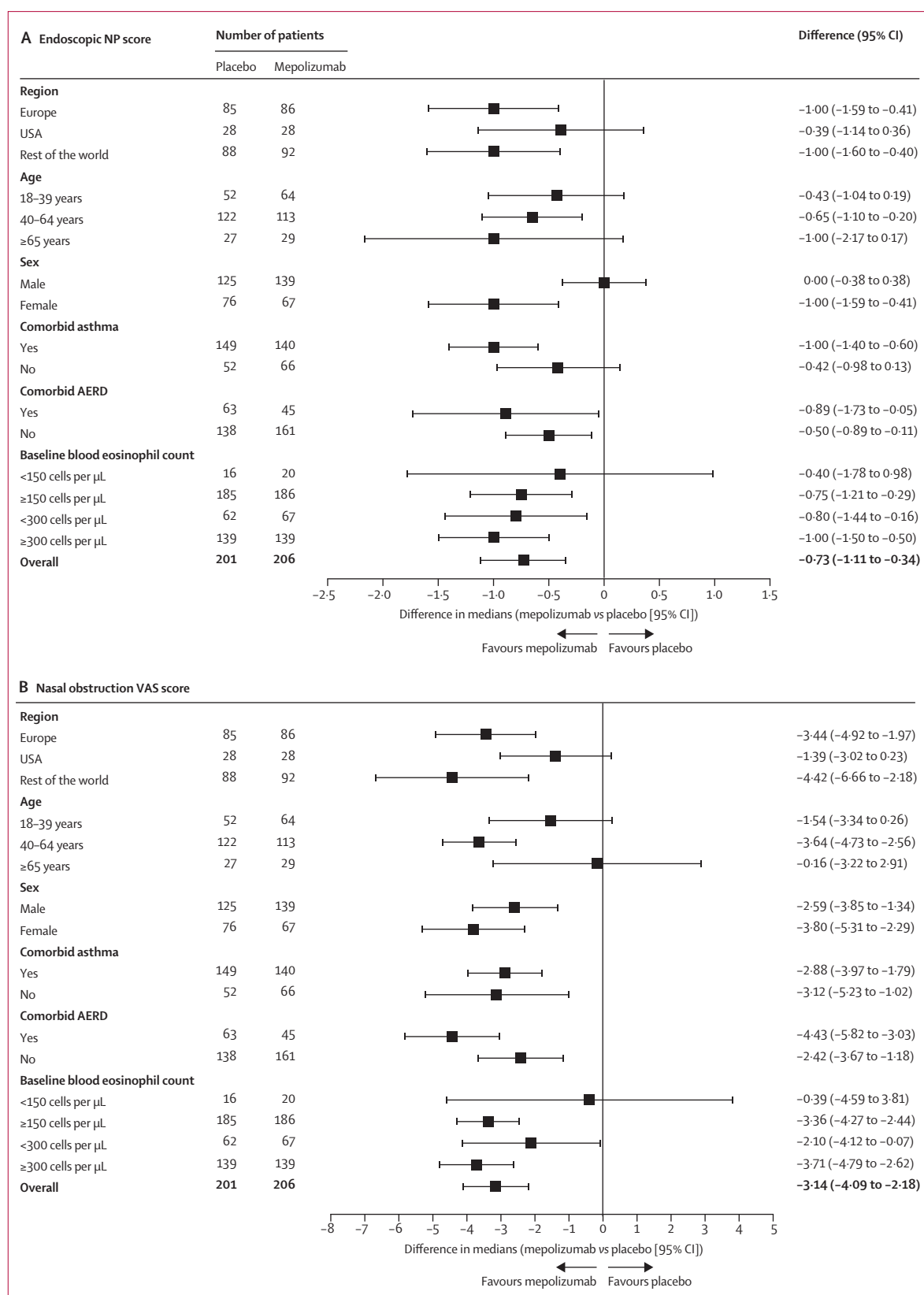


**Figure 2: Change in total endoscopic score and obstruction VAS score in the ITT population**

(A) Total nasal polyp score (week 52). (B) Nasal obstruction VAS score (weeks 49–52). Patients with nasal surgery, those with no nasal surgery who withdrew, and those with missing data before the visit or time period were assigned their worst observed score before surgery, before study withdrawal, or before the missing visit. ITT=intention-to-treat. VAS=visual analogue score.

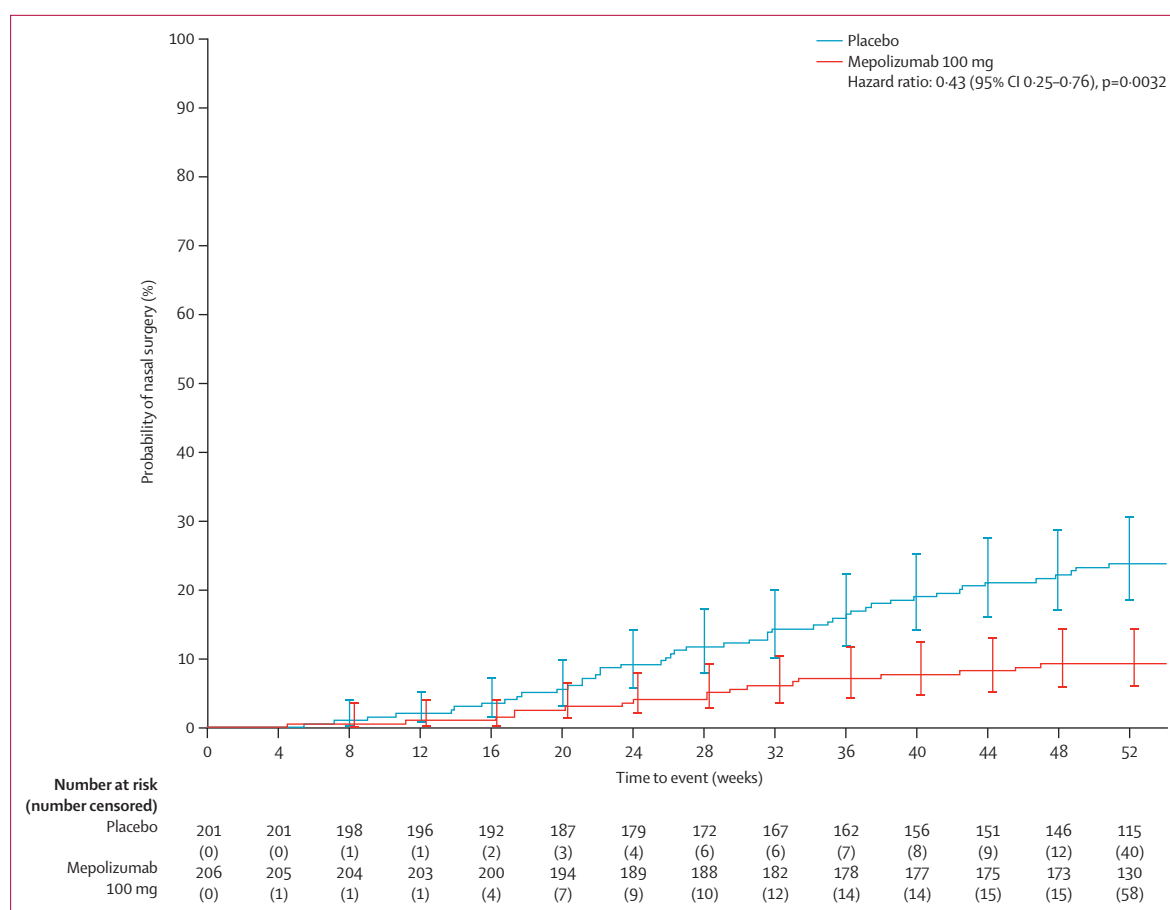
baseline with mepolizumab versus placebo (adjusted difference in median scores based on quantile regression  $-0.73$ , 95% CI  $-1.11$  to  $-0.34$ ;  $p<0.0001$ ; table 2) and nasal obstruction VAS score during weeks 49–52 also significantly improved ( $-3.14$ ,  $-4.09$  to  $-2.18$ ;  $p<0.0001$ ). For total endoscopic nasal polyp score, 104 (50%) of 206 patients receiving mepolizumab versus 57 (28%) of 201 receiving placebo had a 1-point or higher improvement from baseline at week 52, and 74 (36%) versus 26 (13%), respectively, had a 2-point or higher improvement (figure 2; appendix p 10). For nasal obstruction VAS score, 146 (71%) patients receiving mepolizumab versus 100 (50%) receiving placebo had an improvement of more than 1-point from baseline during weeks 49–52; 124 (60%) versus 73 (36%) had an improvement of more than 3-points; and 91 (44%) versus 46 (23%) had an improvement of more than 5-points (figure 2; appendix p 10).

Post-hoc analysis of the mean change from baseline over time in coprimary endpoints is shown in the



**Figure 3: Subgroup analyses of the coprimary endpoints**  
Quantile regression with covariates of treatment group, geographical region, baseline score and log<sub>e</sub> baseline blood eosinophil count.  
AERD=aspirin-exacerbated respiratory disease. VAS=visual analogue score.





**Figure 4: Kaplan-Meier plot of time-to-first nasal surgery (intention-to-treat population)**

Patients with nasal surgery; placebo 46 (23%) and mepolizumab 18 (9%).

appendix (pp 11, 15). Efficacy of mepolizumab versus placebo for the coprimary endpoints stratified by region, age, sex, presence of comorbid asthma, presence of comorbid AERD, and baseline blood eosinophil count is shown in figure 3 (appendix p 2). Subgroup analyses favoured mepolizumab over placebo for most subgroups analysed.

During the 52-week treatment period, the risk of nasal surgery was significantly lower with mepolizumab versus placebo (18 [9%] vs 46 [23%] patients underwent surgery; hazard ratio [HR] 0.43, 95% CI 0.25–0.76;  $p=0.0032$ ; table 2; figure 4; appendix p 16). In terms of systemic corticosteroids courses, 52 (25%) patients in the mepolizumab group and 74 (37%) in the placebo group had received one or more courses of systemic corticosteroids for nasal polyps by week 52 (odds ratio [OR] 0.58, 95% CI 0.36–0.92;  $p=0.020$ ; table 2; appendix p 16); patients in the mepolizumab group received a total of 82 courses (mean prednisolone equivalent dose 109 mg per year [SD 257]) whereas patients in the placebo group received a total of 124 courses (181 mg per year [364]). Overall, 84 (41%) patients receiving mepolizumab versus 100 (50%) receiving placebo required a course of antibiotics (appendix p 16).

For secondary endpoints, the change from baseline in overall symptom VAS score, composite VAS score, and loss of smell VAS score during weeks 49–52, and SNOT-22 total score at week 52 had significantly improved in the mepolizumab group versus the placebo group (table 2; appendix p 13). Improvements in loss of smell were greater in patients with fewer previous surgeries (appendix p 17).

At week 52, the proportion of patients with a 1-point or higher improvement from baseline in total endoscopic nasal polyp score was significantly higher with mepolizumab versus placebo (104 [50%] vs 57 [28%]; OR 2.74, 95% CI 1.80–4.18;  $p<0.0001$ ), and the proportion with a 8.9-point or higher improvement in SNOT-22 score in the absence of surgery was also significantly higher (150 [73%] vs 106 [54%]; 2.44, 1.60–3.73;  $p<0.0001$ ), as was the proportion of patients no longer needing surgery (according to VAS symptom score  $\leq 7$ ) during weeks 49–52, total endoscopic score  $< 5$  at week 52 or no nasal surgery during the treatment period, or both; 149 [72%] vs 103 [51%]; 2.46, 1.59–3.79;  $p<0.0001$ ; appendix p 18).

Improvements from baseline in peak nasal inspiratory flow were greater with mepolizumab versus placebo

	Placebo (n=201)	Mepolizumab (n=206)
<b>All adverse events</b>		
Any on-treatment event	168 (84%)	169 (82%)
Treatment-related event	19 (9%)	30 (15%)
Leading to treatment discontinuation	4 (2%)	4 (2%)
Leading to study withdrawal	1 (1%)	0
<b>Serious adverse events</b>		
Any on-treatment event	13 (6%)	12 (6%)
Treatment-related event*	1 (1%)	0
Resulting in death†	1 (1%)	0
<b>Systemic or local injection-site reactions</b>		
Systemic reaction	1 (1%)	2 (1%)
Local injection-site reaction	2 (1%)	5 (2%)
Anaphylaxis	0	0
<b>Most common adverse events‡</b>		
Nasopharyngitis	46 (23%)	52 (25%)
Headache	44 (22%)	37 (18%)
Epistaxis	18 (9%)	17 (8%)
Sinusitis	22 (11%)	10 (5%)
Back pain	14 (7%)	15 (7%)
Acute sinusitis	13 (6%)	13 (6%)
Oropharyngeal pain	10 (5%)	16 (8%)
Upper respiratory tract infection	14 (7%)	12 (6%)
Nasal polyps	16 (8%)	8 (4%)
Bronchitis	13 (6%)	10 (5%)
Asthma	18 (9%)	4 (2%)
Cough	13 (6%)	7 (3%)
Arthralgia	5 (2%)	13 (6%)
Otitis media	10 (5%)	5 (2%)
*Transient ischaemic attack. †Due to myocardial infarction during the follow-up period. ‡Reported in 5% or more patients in any treatment group.		
<b>Table 3: Summary of adverse events (safety population)</b>		

(adjusted difference in medians 23·1, 95% CI 10·2–36·0;  $p<0\cdot0001$ ; appendix p 18). Changes in UPSIT in a subset of patients ( $n=54$  per treatment group) were not statistically significant between treatment groups (mean change from baseline 1·7 [SD 10·8] for mepolizumab vs 0·4 [8·6] for placebo; adjusted difference in medians 0·40, 95% CI –1·49 to 2·28;  $p=0\cdot30$ ; appendix p 18). Reductions in blood eosinophil counts were significantly greater with mepolizumab versus placebo at all timepoints, with an 81% reduction with mepolizumab versus placebo by week 4 (ratio to placebo 0·19, 0·17–0·22;  $p<0\cdot0001$ ), which was maintained to week 52 (appendix p 14).

In terms of safety analysis, the proportion of patients who had on-treatment adverse events was similar between the two groups (169 [82%] in the mepolizumab group and 168 [84%] in the placebo group; table 3). The most frequently reported adverse events were nasopharyngitis, headache, epistaxis, and sinusitis. Adverse events considered related to study treatment by the investigator were reported in 30 (15%) patients receiving mepolizumab and 19 (9%) receiving placebo.

On-treatment serious adverse events occurred in 12 (6%) patients receiving mepolizumab and 13 (6%) receiving placebo; none were considered related to mepolizumab. One death was reported in the placebo group (myocardial infarction occurring 99 days after the patient's last dose of study treatment); this death was not considered related to treatment. Six patients in the mepolizumab group and three in the placebo group were positive for anti-drug antibodies up to week 52. Of these patients, one patient in the mepolizumab and two in the placebo group were positive for anti-drug antibodies at baseline. Titre values were low, and no patients were positive for neutralising antibodies.

## Discussion

This phase 3 SYNAPSE study shows the efficacy and safety of add-on mepolizumab to standard of care in patients with recurrent, refractory, severe, bilateral chronic rhinosinusitis with nasal polyps who were eligible for repeat nasal surgery. Because all patients had one or more nasal surgery before study entry, their chronic rhinosinusitis with nasal polyps was considered refractory to medical and surgical treatment. Both coprimary endpoints showed a significant benefit at 52 weeks with mepolizumab compared with placebo in addition to standard of care (including systemic corticosteroids as required); polyp size significantly reduced, although median nasal polyp scores were lower at baseline in the mepolizumab versus placebo group, and nasal obstruction symptoms significantly improved. Additionally, mepolizumab significantly reduced the occurrence of nasal surgeries and the use of systemic corticosteroids compared with placebo, and improved nasal symptoms, including loss of smell, which is one of the most bothersome symptoms for patients.<sup>27</sup> Treatment benefits were also supported by improvements in peak nasal inspiratory flow. Health-related quality of life also significantly improved with mepolizumab versus placebo with a between-treatment reduction almost twice the 8·9-point or higher minimal clinically important difference for SNOT-22 score.<sup>24</sup> Treatment effects were seen at 4 weeks after the first dose and were sustained until week 52. The safety profile of mepolizumab was similar to that seen in previous studies, with no new safety indications.<sup>18,19</sup> Although the clinical benefits observed in SYNAPSE are consistent with previous studies<sup>18,19</sup> of intravenous mepolizumab in patients with chronic rhinosinusitis with nasal polyps, this study builds upon previous work and shows efficacy of the 100 mg subcutaneous dose in patients with severe disease who have not responded to standard of care treatment and are eligible for repeat surgery.

The patient population in SYNAPSE reflects a population who are candidates for biological treatment. The 2019 European Forum for Research and Education in Allergy and Airway Diseases expert team proposed that biological treatment should be indicated in patients

with bilateral nasal polyps who have undergone surgery in the past and meet at least three of the following criteria: evidence of T2 inflammation, need for systemic corticosteroids in the past 2 years, substantial quality of life impairment, and a significant loss of smell or a diagnosis of comorbid asthma;<sup>28</sup> the eligibility requirement for previous surgery in SYNAPSE is in line with these recommendations. The reduction in the proportion of patients who received nasal surgery during the study was in line with the EPOS 2020 recommendation to reduce surgery.<sup>2</sup> Moreover, the low systemic corticosteroid use during the 52-week treatment period in patients who received mepolizumab is in line with EPOS 2020, which recommends minimising systemic corticosteroid courses to fewer than two per year in partly controlled or uncontrolled nasal polyps.<sup>2</sup>

Multiple endoscopic nasal surgeries can reduce sense of smell.<sup>29,30</sup> Therefore, the history of repeated nasal surgery in the SYNAPSE population probably contributed to the modest improvements seen in loss of smell VAS scores in the overall patient population. Particularly those with a history of fewer surgeries showed greater improvements in sense of smell, which has also been observed in a previous study.<sup>30</sup> Given that sense of smell is an important outcome to patients,<sup>27</sup> this finding emphasises the need for treatments that reduce repeat surgeries. Improvements in UPSIT, an objective measure of sense of smell, were not statistically significant, most likely because of the small sample size for this endpoint.

Dupilumab, an anti-IL-4 receptor antibody, and omalizumab, an anti-IgE antibody, are also efficacious in patients with chronic rhinosinusitis with nasal polyps, as shown in the SINUS<sup>31</sup> and POLYP<sup>32</sup> studies. Although, previous surgery was not a requirement for inclusion in either of these studies, previous surgery was reported in 63% patients in the SINUS study and 60% in the POLYP study; 15% had three or more previous surgeries in SINUS<sup>31</sup> and 30% had two or more previous surgeries in POLYP.<sup>32</sup> By comparison, all patients in SYNAPSE had one or more previous surgeries at enrolment, 54% of patients had two or more previous surgeries, and 30% had three or more previous surgeries. As such, the population in SYNAPSE might be considered to have more severe and treatment refractory disease than those in the SINUS<sup>31</sup> or the POLYP<sup>32</sup> studies, on the basis of previous need for surgeries in all patients. Additionally, in the SINUS study,<sup>31</sup> patients who received systemic corticosteroids had their worst pre-systemic corticosteroid endpoint value used for analysis, whereas in SYNAPSE values following systemic corticosteroid use were included in the analysis because systemic corticosteroid use was considered a part of standard of care. This difference could have improved endpoint scores for patients in the placebo group (thus reducing the treatment difference *vs* mepolizumab) in SYNAPSE, because patients in the placebo group had greater systemic corticosteroid use compared with patients in

the mepolizumab group. Indeed, improvements in VAS symptom scores and SNOT-22 score with placebo suggested a relatively high treatment response in the placebo group in SYNAPSE versus the SINUS study.<sup>31</sup> As such, SYNAPSE results represent the efficacy of a biological treatment when added to standard of care (including systemic corticosteroids). Finally, there were also differences in the way symptoms were measured across the studies; SYNAPSE used a 100-point VAS scale, whereas the SINUS and POLYP studies used a categorical 4-point scale for each symptom; this difference allowed for greater granularity in the symptom scores in SYNAPSE. All these differences in patient populations and analysis methods highlight why caution is required in any indirect comparisons between the SYNAPSE and the SINUS or POLYP studies.

SYNAPSE showed significant between-treatment differences for coprimary and all secondary endpoints. When comparing the results of SYNAPSE to previous phase 2 studies<sup>18,19</sup> of mepolizumab, the treatment effect size might appear numerically smaller for SYNAPSE. However, there are several differences in study design. For example, assessment of nasal polyp size was done by investigators during the phase 2 studies whereas the same assessment was done by independent, masked reviewers at a central laboratory in SYNAPSE. Although two different doses were used between the phase 2 studies and this phase 3 study, data from a previous study<sup>33</sup> in patients with asthma showed that response to mepolizumab was independent of administration route. Additionally, that study<sup>33</sup> showed that blood eosinophil counts were reduced to a similar amount with the 100 mg subcutaneous dose compared with the 75 mg intravenous dose, indicating that there is substantial pharmacological overlap between the doses. Because the clinical impact of mepolizumab in reducing blood eosinophil count was consistent across the phase 2 studies and SYNAPSE, the dose and route of administration are unlikely to have contributed to the differences observed between the phase 2 and phase 3 studies.

Subgroup analyses of the coprimary endpoints suggested that the efficacy of mepolizumab is higher with higher baseline blood eosinophil count, whereas treatment effects for coprimary endpoints were similar across subgroups stratified by region, age, comorbid asthma, or comorbid AERD. Blood eosinophil count is a biomarker for clinical response in asthma;<sup>34,35</sup> however, unlike previous trials in asthma,<sup>36–38</sup> patients with chronic rhinosinusitis with nasal polyps in SYNAPSE were not selected on the basis of blood eosinophil count. Patient numbers in the baseline blood eosinophil subgroups were low, and in some cases insufficient to accurately determine the effect of eosinophil count on the response to mepolizumab. Although modelling of predicted median change in nasal obstruction VAS score at weeks 49–52 suggested that higher baseline blood eosinophil counts are predictive of a larger treatment

effect, this prediction was not the case for total nasal polyp score. As such, further research is required to investigate blood eosinophil counts as a potential biomarker for the response to mepolizumab in patients with chronic rhinosinusitis with nasal polyps.

In terms of handling surgical events in the analyses, patients who had a surgery during SYNAPSE were assigned their worst observed score before the surgery for coprimary and symptom or health-related quality of life endpoints. This method probably affected patients in the placebo group disproportionately because they typically had more and earlier nasal surgeries than did those receiving mepolizumab. The use of worst observed score for those having surgery was prespecified and reflects the fact that nasal surgery is a poor outcome in patients with chronic rhinosinusitis with nasal polyps. We recognise that alternative strategies for handling these important post-randomisation events could have been considered; however, the effect of the analysis strategy on treatment effect estimates was minimised by using comparisons based on median change from baseline rather than mean change from baseline. Use of medians, rather than means, reduces the influence of extremes in the data. However, even with the placebo response, mepolizumab significantly improved nasal polyp size and symptoms associated with chronic rhinosinusitis with nasal polyps.

There are several potential limitations for this study. First, nasal polyp size determination can be subjective in routine clinical practice, especially when the assessor might be influenced by the knowledge of the patient's symptom during an endoscopic examination. Therefore, to counteract this potential bias, SYNAPSE used independent centrally masked reviewers to score the nasal polyp size and minimise any subjectivity and variability of this assessment. Second, if a patient met the criteria for surgery during the study, the decision to prescribe another course of systemic corticosteroids or proceed to surgery was decided by the physician, who would have been influenced by many subjective factors beyond treatment failure, including surgeon preference, patient desire, and comorbidities. Third, nasal polyp size was not assessed using CT and would have been of interest. We believe CT scans are unlikely to take priority over nasal endoscopy in the assessment of response to systemic therapy, such as a biological treatment, or for the evaluation of polyp recurrence after surgeries, due to the limitations of CT scans, including the inability to delineate polyp and nasal turbinate tissue. As a less invasive and less burdensome procedure, nasal endoscopy is probably used more often given the suggested better correlation of its findings than those of CT scans in a postoperative population similar to that in this study.<sup>39</sup> Moreover, CT scans are not mandated for the initiation or assessment of the response to treatment with a biological therapy according to recent publications.<sup>2,28</sup> Finally, because the type of nasal surgery

(eg, simple polypectomy vs endoscopic sinus surgery vs extended surgery) can affect the risk of nasal polyp reoccurrence, imbalances between treatment groups in the types of previous surgery received could have influenced results;<sup>40</sup> however, this factor was largely controlled for because the patients were randomly assigned to treatment. In conclusion, this phase 3 study showed the efficacy of mepolizumab with an acceptable safety profile in adults with severe chronic rhinosinusitis with nasal polyps.

#### Contributors

JKH, CB, WF, MD, MW, SEL, and CH contributed to the acquisition of study data, data analysis, and interpretation. BM, ARS, and RC contributed to the conceptualisation, study design, data analysis, and interpretation. SGS, NM, and SWY contributed to the data analysis and interpretation. All authors developed, revised, and critically reviewed the manuscript, and provided final approval of the version submitted for publication. All authors participated in the development of the manuscript and had access to the study data. Authors were provided the data at the initial call to discuss the manuscript. All authors are accountable for the accuracy and integrity of the work. BM, RC, and ARS have accessed and verified all the data in the study.

#### Declaration of interests

JKH has received consultancy fees from Sanofi Genzyme, Regeneron, Genentech, AstraZeneca, GlaxoSmithKline, and Gossamer Bio. CB has participated in advisory boards and received speaker fees from Sanofi, Novartis, AstraZeneca, GlaxoSmithKline, ALK-Abelló, and Meda Pharmaceuticals. WF has received clinical trial funding from Sanofi, Mylan, ALK-Abelló, Allergy Therapeutics, Novartis, and Chordate; and personal fees from Sanofi. MD has received clinical trial funding from AstraZeneca, GlaxoSmithKline, Probionase Therapies, and Sanofi; is an advisory board member for Regeneron Pharmaceuticals and Sanofi; and has equity in Probionase Therapies. MW has received advisory board fees or speaker fees from ALK-Abelló, Allergopharma, AstraZeneca, Bencard Allergie, Genzyme, HAL Allergie, InfectoPharm, LETIPharma, Meda Pharmaceuticals, Novartis, Sanofi, Stallergenes Greer, and Teva. SEL has participated in advisory boards and received clinical trial funding from Sanofi Genzyme, Regeneron, Genentech, AstraZeneca, and GlaxoSmithKline. SGS, NM, BM, SWY, ARS, and RC are employees of GlaxoSmithKline and own company stocks and shares. CH has received advisory board fees from Sanofi, AstraZeneca, Olympus, and Smith and Nephew.

#### Data sharing

Anonymised individual participant data and study documents can be requested for further research from <http://www.clinicalstudydatarequest.com>. The trial protocol and statistical analysis plan are available at <https://www.gsk-studyregister.com/>.

#### Acknowledgments

We thank the patients who took part in the study. This study was funded by GlaxoSmithKline (GSK ID: 205687; NCT03085797). Editorial support (in the form of writing assistance, including preparation of the draft manuscript under direction and guidance of the authors, collating and incorporating authors' comments for each draft, assembling tables and figures, grammatical editing and referencing) was provided by Elizabeth Hutchinson (Fishawack Indicia, Knutsford, UK, part of Fishawack Health) and funded by GlaxoSmithKline.

#### References

- Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int J Epidemiol* 1999; **28**: 717–22.
- Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and nasal polyps 2020. *Rhinology* 2020; **58** (suppl S29): 1–464.
- Bachert C, Wagenmann M, Hauser U, Rudack C. IL-5 synthesis is upregulated in human nasal polyp tissue. *J Allergy Clin Immunol* 1997; **99**: 837–42.

- 4 Bachert C, Zhang N, Cavaliere C, Weiping W, Gevaert E, Krysko O. Biologics for chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol* 2020; **145**: 725–39.
- 5 Bachert C, Zhang N, Holtappels G, et al. Presence of IL-5 protein and IgE antibodies to staphylococcal enterotoxins in nasal polyps is associated with comorbid asthma. *J Allergy Clin Immunol* 2010; **126**: 962–68.
- 6 Hamilos DL, Leung DY, Huston DP, Kamil A, Wood R, Hamid Q. GM-CSF, IL-5 and RANTES immunoreactivity and mRNA expression in chronic hyperplastic sinusitis with nasal polyposis (NP). *Clin Exp Allergy* 1998; **28**: 1145–52.
- 7 Kohli P, Naik AN, Harruff EE, Nguyen SA, Schlosser RJ, Soler ZM. The prevalence of olfactory dysfunction in chronic rhinosinusitis. *Laryngoscope* 2017; **127**: 309–20.
- 8 Alobid I, Bernal-Sprekelsen M, Mullol J. Chronic rhinosinusitis and nasal polyps: the role of generic and specific questionnaires on assessing its impact on patient's quality of life. *Allergy* 2008; **63**: 1267–79.
- 9 Alobid I, Cardelus S, Benítez P, et al. Persistent asthma has an accumulative impact on the loss of smell in patients with nasal polyposis. *Rhinology* 2011; **49**: 519–24.
- 10 Hox V, Lourijsen E, Jordens A, et al. Benefits and harm of systemic steroids for short- and long-term use in rhinitis and rhinosinusitis: an EAACI position paper. *Clin Transl Allergy* 2020; **10**: 1.
- 11 DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Laryngoscope* 2017; **127**: 550–55.
- 12 Hosemann W. Surgical treatment of nasal polyposis in patients with aspirin intolerance. *Thorax* 2000; **55** (suppl 2): S87–90.
- 13 Alanin MC, Laidlaw T, Society TS, Hopkins C. The burden of non-steroidal anti-inflammatory exacerbated respiratory disease from the patient's perspective - a qualitative analysis of posts from the Samter's Society. *Rhinology* 2020; **58**: 333–40.
- 14 Vennik J, Eyles C, Thomas M, et al. Management strategies for chronic rhinosinusitis: a qualitative study of GP and ENT specialist views of current practice in the UK. *BMJ Open* 2018; **8**: e022643.
- 15 Flood-Page P, Menzies-Gow A, Phipps S, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J Clin Invest* 2003; **112**: 1029–36.
- 16 European Medicines Agency. Mepolizumab summary of product characteristics. March, 2021. [https://www.ema.europa.eu/en/documents/product-information/nucala-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/nucala-epar-product-information_en.pdf) (accessed March 30, 2021).
- 17 GlaxoSmithKline. Mepolizumab prescribing information. September, 2020. [https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing\\_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF](https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF) (accessed March 30, 2021).
- 18 Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol* 2011; **128**: 989–95.
- 19 Bachert C, Sousa AR, Lund VJ, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. *J Allergy Clin Immunol* 2017; **140**: 1024–31.e14.
- 20 GlaxoSmithKline. Effect of mepolizumab in severe bilateral nasal polyps. <https://www.gsk-studyregister.com/en/trial-details/?id=205687> (accessed Dec 1, 2020).
- 21 Hopkins C. Chronic rhinosinusitis with nasal polyps. *N Engl J Med* 2019; **381**: 55–63.
- 22 van der Veen J, Seys SF, Timmermans M, et al. Real-life study showing uncontrolled rhinosinusitis after sinus surgery in a tertiary referral centre. *Allergy* 2017; **72**: 282–90.
- 23 Xu Z, Luo X, Xu L, et al. Effect of short-course glucocorticoid application on patients with chronic rhinosinusitis with nasal polyps. *World Allergy Organ J* 2020; **13**: 100131.
- 24 Chowdhury NI, Mace JC, Bodner TE, et al. Investigating the minimal clinically important difference for SNOT-22 symptom domains in surgically managed chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2017; **7**: 1149–55.
- 25 Keene ON. Strategies for composite estimands in confirmatory clinical trials: examples from trials in nasal polyps and steroid reduction. *Pharm Stat* 2019; **18**: 78–84.
- 26 Mehrotra DV, Liu F, Permutt T. Missing data in clinical trials: control-based mean imputation and sensitivity analysis. *Pharm Stat* 2017; **16**: 378–92.
- 27 Chung JH, Lee YJ, Kang TW, et al. Altered quality of life and psychological health (SCL-90-R) in patients with chronic rhinosinusitis with nasal polyps. *Ann Otol Rhinol Laryngol* 2015; **124**: 663–70.
- 28 Bachert C, Han JK, Wagenmann M, et al. EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: definitions and management. *J Allergy Clin Immunol* 2021; **147**: 29–36.
- 29 Nguyen DT, Bey A, Arous F, Nguyen-Thi PL, Felix-Ravelo M, Jankowski R. Can surgeons predict the olfactory outcomes after endoscopic surgery for nasal polyposis? *Laryngoscope* 2015; **125**: 1535–40.
- 30 Seys SF, De Bont S, Fokkens WJ, et al. Real-life assessment of chronic rhinosinusitis patients using mobile technology: the mySinusitisCoach project by EUFOREA. *Allergy* 2020; **75**: 2867–78.
- 31 Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet* 2019; **394**: 1638–50.
- 32 Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol* 2020; **146**: 595–605.
- 33 Pouliquen IJ, Kornmann O, Barton SV, Price JA, Ortega HG. Characterization of the relationship between dose and blood eosinophil response following subcutaneous administration of mepolizumab. *Int J Clin Pharmacol Ther* 2015; **53**: 1015–27.
- 34 Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med* 2016; **4**: 549–56.
- 35 Yancey SW, Keene ON, Albers FC, et al. Biomarkers for severe eosinophilic asthma. *J Allergy Clin Immunol* 2017; **140**: 1509–18.
- 36 Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; **371**: 1189–97.
- 37 Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; **371**: 1198–207.
- 38 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. *Lancet Respir Med* 2017; **5**: 390–400.
- 39 Ryan WR, Ramachandra T, Hwang PH. Correlations between symptoms, nasal endoscopy, and in-office computed tomography in post-surgical chronic rhinosinusitis patients. *Laryngoscope* 2011; **121**: 674–78.
- 40 Noon E, Hopkins C. Review article: outcomes in endoscopic sinus surgery. *BMC Ear Nose Throat Disord* 2016; **16**: 9.