Mepolizumab for chronic rhinosinusitis with nasal polyps: Treatment efficacy by comorbidity and blood eosinophil count

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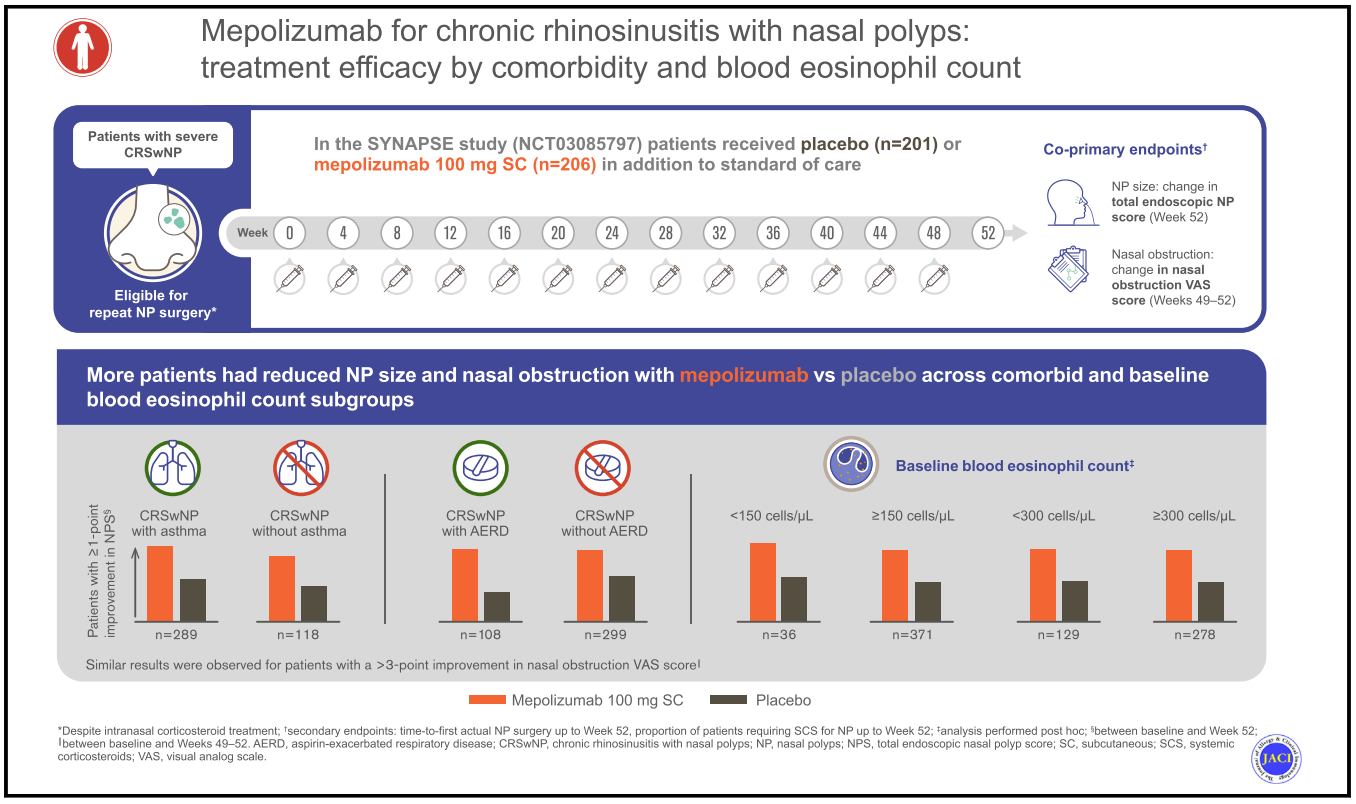
GRAPHICAL ABSTRACT



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Background: In the phase III SYNAPSE study, mepolizumab reduced nasal polyp (NP) size and nasal obstruction in chronic rhinosinusitis with NP.

Objective: We sought to assess the efficacy of mepolizumab in patients from SYNAPSE grouped by comorbid asthma, aspirin-exacerbated respiratory disease (AERD), and baseline blood eosinophil count (BEC).

Methods: SYNAPSE, a randomized, double-blind, 52-week study (NCT03085797), included patients with severe bilateral chronic rhinosinusitis with NP eligible for surgery despite intranasal corticosteroid treatment. Patients received 4-weekly subcutaneous mepolizumab 100 mg or placebo plus standard of care for 52 weeks. Coprimary end points were change in total endoscopic NP score (week 52) and nasal obstruction visual analog scale score (weeks 49-52). Subgroup analyses by comorbid asthma and AERD status, and *post hoc* by BEC, were exploratory.

Results: Analyses included 407 patients (289 with asthma; 108 with AERD; 371 and 278 with BEC counts ≥150 or ≥300 cells/μL, respectively). The proportion of patients with greater than or equal to 1-point improvement from baseline in NP score was higher with mepolizumab versus placebo across comorbid diseases (asthma: 52.9% vs 29.5%; AERD: 51.1% vs 20.6%) and baseline BEC subgroups (<150 cells/μL: 55.0% vs 31.3%; ≥150 cells/μL: 49.5% vs 28.1%; <300 cells/μL: 50.7% vs 29.0%; ≥300 cells/μL: 50.4% vs 28.1%). A similar trend was observed in patients without comorbid asthma or AERD. More patients had more than 3-point improvement in nasal obstruction VAS score with mepolizumab versus placebo across comorbid subgroups.

Conclusions: Mepolizumab reduced polyp size and nasal obstruction in chronic rhinosinusitis with NP regardless of the presence of comorbid asthma or AERD. (J Allergy Clin Immunol 2022;149:1711-21.)

Key words: *Asthma, blood eosinophils, chronic rhinosinusitis, biologic therapy, mepolizumab, nasal polyps, AERD, type 2 inflammation, sinus surgery*

Abbreviations used

ACQ-5: 5-item Asthma Control Questionnaire
AE: Adverse event
AERD: Aspirin-exacerbated respiratory disease
CRSwNP: Chronic rhinosinusitis with nasal polyps
ITT: Intent-to-treat
MCID: Minimum clinically important difference
NP: Nasal polyp
SC: Subcutaneous
SCS: Systemic corticosteroid
SNOT-22: 22-item Sino-Nasal Outcomes Test
SoC: Standard of care
VAS: Visual analog scale

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a clinical diagnosis that affects approximately 4% of the adult population in postindustrialized countries and is one of the most severe forms of chronic rhinosinusitis associated with a significantly impaired health-related quality of life.[1,2] In CRSwNP, chronic inflammation is primarily driven by type 2 proinflammatory cytokines such as IL-5, IL-4, and IL-13 alongside high levels of eosinophils in the surrounding tissue.[3,4] Symptoms mainly include nasal blockage, loss of sense of smell, postnasal drip, facial pressure, and rhinorrhea.[3,5-7]

Standard of care (SoC) treatments include topical intranasal corticosteroids, short courses of systemic corticosteroids (SCS), and endoscopic sinus surgery.[3,6,8] These treatment options may offer short-term symptom relief; however, the use of SCS is associated with significant adverse events (AEs) and although endoscopic sinus surgery is successful in up to 85% of patients with CRS, patients with severe CRSwNP who have had endonasal surgery experience a 40% recurrence rate over 3 years and up to 80% over 12 years.[9-11] As such, additional treatment options are needed.

Patients with severe CRSwNP and comorbid asthma, aspirin-exacerbated respiratory disease (AERD), and patients who present with eosinophilic infiltration experience the greatest burden of disease. Of significance, these patients experience greater numbers of sinus surgeries, high corticosteroid use, and long-term disease recurrence with SoC than patients without these disease characteristics.[9,11-14] Importantly, patients with asthma and AERD represent 23% to 45%[15-17] and 10% to 16%[12,16] of patients with severe CRSwNP, respectively. The European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) suggests that patients with severe CRSwNP and comorbid asthma or patients with a blood eosinophil count >300 cells/μL are more likely to present with type 2 inflammation, and as such may benefit from type 2 biologic

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Data sharing statement: Anonymized individual participant data and study documents for the parent study can be requested for further research from www.clinicalstudydatarequest.com.

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therapy (eg, anti–IL-4/receptor alpha and anti–IL-5/receptor alpha).[18] In addition, previous mepolizumab trials in severe eosinophilic asthma suggest that patients with a blood eosinophil count ≥150 cells/μL at baseline were more likely to benefit from mepolizumab therapy.[19,20]

Mepolizumab is a targeted, humanized anti–IL-5 mAb that prevents IL-5 from binding to its receptor on eosinophils, and selectively inhibits eosinophilic inflammation.[21] Mepolizumab (100 mg administered subcutaneously [SC]) is approved for the treatment of severe eosinophilic asthma and CRSwNP and at a dose of 300 mg for patients with eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndrome in multiple countries worldwide.[22,23]

The phase III SYNAPSE study demonstrated that mepolizumab reduced nasal polyp (NP) size and ameliorated symptoms of nasal obstruction, decreased actual nasal surgery rates and SCS use, improved sinonasal symptoms in patients with severe CRSwNP, and had an acceptable safety profile.[24] In addition, initial results from SYNAPSE suggested that mepolizumab was efficacious in improving nasal obstruction in patients with a high baseline blood eosinophil count,[24] in line with mepolizumab's IL-5 binding and eosinophil-blocking mechanism of action.[21] Similar observations have been reported in patients with asthma and chronic obstructive pulmonary disease.[19,25] The aim of this exploratory analysis was to assess the efficacy of mepolizumab compared with placebo in adults with severe, bilateral CRSwNP requiring revision surgery, stratified by the presence of comorbid asthma, comorbid AERD, and baseline blood eosinophil count.

METHODS

Study design

SYNAPSE was a phase III, randomized, double-blind, placebo-controlled, parallel-group study (GlaxoSmithKline ID: 205687; NCT03085797). Full details of this study and eligibility criteria have been published previously.[24] Briefly, following a 4-week run-in period, patients were randomized 1:1 to treatment with mepolizumab 100 mg SC or placebo every 4 weeks for 52 weeks. All patients received SoC throughout the study, consisting of daily mometasone furoate nasal spray, and saline nasal irrigations and short courses of SCS and/or antibiotics, as required. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and the applicable country-specific regulatory requirements. All patients provided written informed consent before any study-related activities. The study was approved by local ethics review boards of the participating sites. The protocol is available at https://www.gsk-studyregister.com/ (GlaxoSmithKline ID: 205687).

Patients

Eligible patients were 18 years or older, with recurrent, severe bilateral NP symptoms (nasal obstruction visual analog scale [VAS] symptom score of >5 out of 10), eligible for repeat nasal surgery (overall VAS symptom score >7 out of 8 and an endoscopic NP score of ≥5 of 8 and with a minimum score of 2 in each nasal cavity), despite SoC. Patients must also have had 1 or more nasal surgery (any procedure involving instruments with resulting polypectomy) in the previous 10 years as well as stable maintenance therapy for 8 or more weeks before screening, and displayed symptoms of CRS for at least 12 weeks before screening (nasal blockage/obstruction/congestion or nasal discharge [anterior/posterior nasal drip], with ≥1 of the following additional symptoms: nasal discharge, facial pain/pressure, or reduction/loss of sense of smell).

End points and assessments

The coprimary end points were change from baseline in total endoscopic NP score at week 52 and change from baseline in nasal obstruction VAS score during weeks 49 to 52. Total endoscopic NP 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), giving a total score of up to 8. VAS scores ranged from 0 to 10. As a minimum clinically important difference (MCID) has not been established for total endoscopic NP score, we reported the proportion of patients with either a 1-point or higher or a 2-point or higher improvement in total endoscopic NP score, in line with the POLYP1 and POLYP2 phase III clinical studies.[18] Likewise, for nasal obstruction VAS score, we reported the proportion of patients with more than 3-point improvement in nasal obstruction VAS score, as previous studies have shown that improvement in VAS scores is associated with meaningful improvement in both quality of life and symptom scores.[26]

The key secondary end point was time-to-first actual nasal surgery up to week 52. Nasal surgery was defined as any procedure involving instruments resulting in the incision of the paranasal sinuses and removal of polyp tissue from the nasal cavity (polypectomy) and the sinuses. Full nasal surgery definitions have been published previously.[24] Other secondary end points included the proportion of patients requiring SCS for NP up to week 52, and change from baseline in overall symptoms VAS score during weeks 49 to 52, 22-item Sino-Nasal Outcomes Test (SNOT-22) total score at week 52, composite VAS score (combining scores for nasal obstruction, nasal discharge, mucus in the throat, and loss of sense of smell) during weeks 49 to 52, and VAS score for loss of sense of smell during weeks 49 to 52. SNOT-22 scores ranged from 0 to 110. Change from baseline in SNOT-22 score of more than 9 points by week 52 is reported (MCID, -8.9 points[27]). In patients with comorbid asthma, *post hoc* analyses included the annual rate of clinically significant exacerbations, change from baseline in 5-item Asthma Control Questionnaire (ACQ-5) score at week 52, and the proportion of patients with a greater than or equal to 0.5 reduction in ACQ-5 score (MCID).[28] A clinically significant asthma exacerbation was defined as a worsening of asthma requiring SCS for 3 or more days or a single intramuscular corticosteroid dose, an emergency department visit, and/or hospitalization.

Safety assessments included monitoring for AE and serious AEs throughout the study.

Statistical analysis

End points were assessed in patients who were randomized and received 1 or more dose of the study drug (intent-to-treat [ITT] population) grouped according to the presence of comorbid asthma (with/without) or comorbid AERD (with/without). The presence of a comorbidity was determined from the patient's medical history, as reported on their electronic case report form. End points were also assessed within the baseline blood eosinophil count thresholds established for severe asthma (<150 or ≥150 cells/μL; <300 or ≥300 cells/μL), and according to the categories of ≤300, >300 to ≤500, >500 to ≤700, or >700 cells/μL.[20,29]

Statistical analyses for this study have been described in detail previously.[24] Briefly, all data reported up to week 52 were included in the analysis, regardless of treatment discontinuation. Patients who underwent nasal surgery before week 52, or who withdrew from the study early or had missing data for any other reason, were assigned their worst observed score before the event (surgery/study withdrawal/missing visit) for all subsequent visits.[24] Use of SCS during the treatment period was considered part of SoC, so observed scores following SCS use were included in the analyses.

Analyses by baseline blood eosinophil thresholds (<150 or ≥150 cells/μL; <300 or ≥300 cells/μL) were performed *post hoc*. For patients with comorbid asthma, *post hoc* analyses included the annual rate of clinically significant exacerbations, and the proportion of patients with a greater than or equal to 0.5 reduction in ACQ-5 score (MCID).

As described by Han et al[24] for the coprimary end points, VAS scores, and SNOT-22 scores, the nonparametric Wilcoxon rank-sum test was used to assess the difference in change from baseline scores between treatment groups.[24] Time-to-first nasal surgery was analyzed using a Cox proportional hazards model. The proportion of patients requiring SCS for NP was analyzed

TABLE I. Baseline demographic and clinical characteristics for patients with or without comorbid asthma or with or without comorbid AERD

	Comorbid asthma				Comorbid AERD			
	With		Without		With		Without	
Characteristic	Placebo (n = 149)	Mepo (n = 140)	Placebo (n = 52)	Mepo (n = 66)	Placebo (n = 63)	Mepo (n = 45)	Placebo (n = 138)	Mepo (n = 161)
Age (y), mean ± SD	48.7 ± 12.2	48.5 ± 13.3	49.4 ± 13.2	48.9 ± 14.3	48.6 ± 11.3	46.8 ± 12.2	49.0 ± 13.0	49.1 ± 13.9
Sex: female, n (%)	65 (43.6)	48 (34.3)	11 (21.2)	19 (28.8)	28 (44.4)	18 (40.0)	48 (34.8)	49 (30.4)
Ethnicity, n (%)								
Hispanic/Latino	20 (13.4)	14 (10.0)	9 (17.3)	10 (15.2)	4 (6.3)	2 (4.4)	25 (18.1)	22 (13.7)
Not Hispanic/Latino	129 (86.6)	126 (90.0)	43 (82.7)	56 (84.8)	59 (93.7)	43 (95.6)	113 (81.9)	139 (86.3)
Race, n (%)								
Central/South Asian Heritage	1 (0.7)	2 (1.4)	0	0	1 (1.6)	0	0	2 (1.2)
East Asian Heritage	7 (4.7)	5 (3.6)	0	1 (1.5)	4 (6.3)	1 (2.2)	3 (2.2)	5 (3.1)
South East Asian Heritage	0	1 (0.7)	1 1.9)	0	0	0	1 (0.7)	1 (0.6)
Black or African American	3 (2.0)	5 (3.6)	1 (1.9)	0	1 (1.6)	1 (2.2)	3 (2.2)	4 (2.5)
Arabic/North African Heritage	3 (2.0)	1 (0.7)	1 (1.9)	1 (1.5)	2 (3.2)	0	2 (1.4)	2 (1.2)
White/Caucasian/ European Heritage	134 (89.9)	126 (90.0)	49 (94.2)	64 (97.0)	55 (87.3)	43 (95.6)	128 (92.6)	147 (91.3)
Multiple	1 (0.7)	0	0	0	0	0	1 (0.7)	0
BMI (kg/m^2), mean ± SD	28.3 ± 5.7	28.0 ± 5.2	27.9 ± 4.8	28.4 ± 5.4	28.8 ± 5.6	28.0 ± 5.6	27.9 ± 5.4	28.2 ± 5.2
Duration of NP (y), mean ± SD	11.4 ± 7.6	11.8 ± 8.0	11.6 ± 10.0	10.5 ± 9.5	13.6 ± 8.7	11.8 ± 8.5	10.5 ± 7.9	11.2 ± 8.6
Previous nasal surgery, n (%)								
0	0 (0)	0 (0)	0 (0)	0(0)	0 (0)	0(0)	0 (0)	0 (0)
≥1	149 (100.0)	140 (100.0)	52 (100.0)	66 (100.0)	63 (100.0)	45 (100.0)	138 (100.0)	161 (100.0)
≥2	95 (63.8)	71 (50.7)	25 (48.1)	27 (40.9)	44 (69.8)	24 (53.3)	76 (55.1)	74 (45.9)
≥3	59 (39.6)	37 (26.4)	14 (26.9)	14 (21.2)	31 (49.2)	14 (31.1)	42 (30.4)	37 (23.0)
≥4	28 (18.8)	18 (12.9)	10 (19.2)	5 (7.6)	21 (33.3)	4 (8.8)	17 (12.3)	20 (12.4)
≥5	19 (12.8)	8 (5.7)	7 (13.5)	3 (4.5)	15 (23.8)	3 (6.7)	11 (8.0)	8 (5.0)
Time since last NP surgery (y), mean ± SD (range)*	3.8 ± 2.6 (0.3-9.9)	4.2 ± 2.8 (0.0-10.3)	3.9 ± 2.8 (0.5-9.5)	4.2 ± 2.4 (0.7-10.7)	3.8 ± 2.8 (0.5-9.9)	4.1 ± 2.6 (0.4-9.7)	3.9 ± 2.6 (0.3-9.8)	4.2 ± 2.7 (0.0-10.7)
OCS courses for NP in previous 12 mo, n (%)								
0	75 (50.3)	58 (41.4)	35 (67.3)	42 (63.6)	33 (52.4)	21 (46.7)	77 (55.8)	79 (49.1)
≥1	74 (49.7)	82 (58.6)	17 (32.7)	24 (36.4)	30 (47.6)	24 (53.3)	61 (44.2)	82 (50.9)
≥2	35 (23.5)	33 (23.6)	9 (17.3)	9 (13.6)	16 (25.4)	10 (22.2)	28 (20.3)	32 (19.9)
Total endoscopic NP score, median (range) (scale: 0-8)	6.0 (0-8)	5.0 (2-8)	5.0 (2-8)	5.0 (2-8)	5.0 (2-8)	6.0 (4-8)	6.0 (0-8)	5.0 (2-8)
Nasal obstruction VAS score, median (range) (scale: 0-10)†	9.2 (6.7-10.0)	9.1 (6.8-10.0)	8.9 (5.3-10.0)	8.9 (6.5-10.0)	9.4 (5.3-10.0)	9.2 (6.8, 10.0)	9.1 (6.3-10.0)	9.0 (6.5-10.0)
Overall VAS symptom score, median (range) (scale: 0-10)†	9.3 (7.3-10.0)	9.2 (7.2-10.0)	9.0 (7.2-10.0)	9.0 (7.5-10.0)	9.4 (7.3-10.0)	9.4 (7.5-10.0)	9.1 (7.2-10.0)	9.1 (7.2-10.0)
Nasal symptom VAS composite‡ score, median (range) (scale: 0-10)†	9.3 (6.0-10.0)	9.2 (6.9-10.0)	9.1 (6.6-10.0)	9.0 (4.9-10.0)	9.4 (6.0-10.0)	9.2 (7.2-10.0)	9.1 (6.6-10.0)	9.0 (4.9-10.0)
Loss of sense of smell VAS score, median (range) (scale: 0-10)†	10.0 (6.7-10.0)	10.0 (0.9-10.0)	9.7 (7.4-10.0)	9.8 (7.7-10.0)	10.0 (8.8-10.0)	10.0 (7.7-10.0)	9.9 (6.7- 10.0)	9.9 (0.9-10.0)
SNOT-22 total score, median (range)†	68.0 (21-107)	67.0 (28-105)	56.5 (19-110)	56.0 (17-88)	72.0 (38-101)	67.0 (28-98)	61.0 (19-110)	62.0 (17-105)
Patients with asthma, n (%)	149 (100.0)	140 (100.0)	0	0	60 (95.2)	43 (95.6)	89 (64.5)	97 (60.2)
Baseline ACQ-5 score, mean ± SD	2.15 ± 1.4	2.38 ± 1.4	NA	NA	NA	NA	NA	NA
Patients with AERD, n (%)	60 (40.3)	43 (30.7)	3 (5.8)	2 (3.0)	63 (100.0)	45 (100.0)	0	0
Blood eosinophil count (cells/μL), geometric mean (SD logs)	430 (0.769)	460 (0.747)	310 (0.747)	270 (0.641)	460 (0.819)	420 (0.874)	370 (0.749)	380 (0.720)

BMI, Body mass index; *mepo*, mepolizumab 100 mg subcutaneous; *OCS*, oral corticosteroid.

*Twenty-five percent of patients in the ITT population had partial dates for previous surgeries. Where partial dates were available, missing day was assumed as the last day of the month and missing month as December.

†Higher scores indicate greater disease severity or worse quality of life.

‡Combining scores for nasal obstruction, nasal discharge, mucus in the throat, and loss of sense of smell.

using a logistic regression model. To control for multiplicity arising from multiple secondary end points, a closed testing procedure was used according to a predefined hierarchy: time-to-first nasal surgery, overall VAS symptom score, SNOT-22 total score, SCS for NP use, composite VAS score, and loss of sense of smell VAS symptom score end points.

RESULTS

Patient population

Of the 407 patients included in the ITT population (mepolizumab, n = 206; placebo, n = 201), 289 had comorbid asthma and 108 had comorbid AERD; of those with comorbid asthma, 103 patients also had comorbid AERD. At baseline, 371 patients had a blood eosinophil count ≥150 cells/μL and 278 patients had ≥300 cells/μL. The number of patients in each subgroup and the overlap between subgroups is presented in Fig E1 in this article's Online Repository at www.jacionline.org.

At baseline, in patients with comorbid asthma, higher SNOT-22 scores, blood eosinophil counts, number of previous surgeries, and proportion of females were observed compared with patients without comorbid asthma; a similar trend was observed in patients with versus without comorbid AERD (Table I). In addition, patients with comorbid asthma had more oral corticosteroid courses for NP in the 12 months before baseline than patients without comorbid asthma (Table I). Patients generally had similar baseline demographic and disease

TABLE II. Baseline demographic and clinical characteristics by baseline blood eosinophil count

	Baseline blood eosinophil count (cells/μL)							
	<150		≥150		<300		≥300	
Characteristic	Placebo (n = 16)	Mepo (n = 20)	Placebo (n = 185)	Mepo (n = 186)	Placebo (n = 62)	Mepo (n = 67)	Placebo (n = 139)	Mepo (n = 139)
Age (y), mean ± SD	50.6 ± 14.4	49.2 ± 13.2	48.7 ± 12.3	48.6 ± 13.6	50.2 ± 12.0	49.3 ± 12.7	48.3 ± 12.7	48.3 ± 14.0
Sex: female, n (%)	5 (31.3)	11 (55.0)	71 (38.4)	56 (30.1)	20 (32.3)	26 (38.8)	56 (40.3)	41 (29.5)
Ethnicity, n (%)								
Hispanic/Latino	3 (18.8)	3 (15.0)	26 (14.1)	21 (11.3)	9 (14.5)	6 (9.0)	20 (14.4)	18 (12.9)
Not Hispanic/Latino	13 (81.3)	17 (85.0)	159 (85.9)	165 (88.7)	53 (85.5)	61 (91.0)	119 (85.6)	121 (87.1)
Race, n (%)								
Central/South Asian Heritage	0	0	1 (0.5)	2 (1.1)	0	0	1 (0.7)	2 (1.4)
East Asian Heritage	0	1 (5.0)	7 (3.8)	5 (2.7)	1 (1.6)	1 (1.5)	6 (4.3)	5 (3.6)
South East Asian Heritage	0	0	1 (0.5)	1 0.5)	0	0	1 (0.7)	1 (0.7)
Black or African American	0	0	4 (2.2)	5 (2.7)	0	2 (3.0)	4 2.9)	3 (2.2)
Arabic/North African Heritage	0	0	4 (2.2)	2 (1.1)	1 (1.6)	1 (1.5)	3 (2.2)	1 (0.7)
White/Caucasian/ European Heritage	15 (93.8)	19 (95.0)	168 (90.8)	171 (91.9)	59 (95.2)	63 (94.0)	124 (89.2)	127 (91.4)
Multiple	1 (6.3)	0	0	0	1 (1.6)	0	0	0
BMI (kg/m^2), mean ± SD	26.6 ± 3.1	25.3 ± 5.0	28.3 ± 5.6	28.5 ± 5.2	27.3 ± 5.7	27.3 ± 4.9	28.5 ± 5.3	28.5 ± 5.4
Duration of NP (y), mean ± SD	12.0 ± 10.4	11.3 ± 10.4	11.4 ± 8.1	11.4 ± 8.3	12.7 ± 9.0	12.1 ± 10.2	10.9 ± 7.9	11.0 ± 7.6
Previous nasal surgery, n (%)								
0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
≥1	16 (100.0)	20 (100.0)	185 (100.0)	186 (100.0)	62 (100.0)	67 (100.0)	139 (100.0)	139 (100.0)
≥2	9 (56.3)	11 (55.0)	111 (60)	87 (46.8)	38 (61.3)	33 (49.3)	82 (59.0)	65 (46.8)
≥3	3 (18.8)	5 (25.0)	70 (38)	46 (24.7)	21 (33.9)	16 (23.9)	62 (44.6)	35 (25.2)
≥4	3 (18.8)	2 (10.0)	35 (19)	22 (11.8)	12 (19.4)	8 (11.9)	26 (18.7)	16 (11.5)
≥5	2 (12.5)	1 (5.0)	24 (13)	10 (5.4)	8 (12.9)	4 (6.0)	18 (12.9)	7 (5.0)
Time since last NP surgery (y), mean ± SD (range)*	4.1 ± 2.7 (1.0-9.9)	4.1 ± 2.6 (0.5-8.8)	3.8 ± 2.7 (0.3-9.8)	4.2 ± 2.7 (0.0-10.7)	4.4 ± 2.8 (0.3-9.9)	4.3 ± 2.6 (0.5-10.7)	3.6 ± 2.6 (0.5-9.7)	4.2 ± 2.7 (0.0-10.3)
OCS courses for NP in previous 12 mo, n (%)								
0	10 (62.5)	12 (60.0)	100 (54.1)	88 (47.3)	41 (66.1)	40 (59.7)	69 (49.6)	60 (43.2)
≥1	6 (37.5)	8 (40.0)	85 (45.9)	98 (52.7)	21 (33.9)	27 (40.3)	70 (50.4)	79 (56.8)
≥2	3 (18.8)	3 (15.0)	41 (22.2)	39 (21.0)	10 (16.1)	9 (13.4)	34 (24.5)	33 (23.7)
Total endoscopic NP score, median (range) (scale: 0-8)	5.5 (2-7)	5.0 (2-8)	6.0 (0-8)	5.0 (2-8)	5.0 (2-8)	5.0 (2-8)	6.0 (0-8)	5.0 (2-8)
Nasal obstruction VAS score, median (range) (scale: 0-10)†	9.0 (7.7-10.0)	9.3 (6.8-10.0)	9.2 (5.3-10.0)	9.0 (6.5-10.0)	8.9 (7.0-10.0)	9.0 (6.8-10.0)	9.2 (5.3-10.0)	9.0 (6.5-10.0)
Overall VAS symptom score, median (range) (scale: 0-10)†	9.0 (8.3-10.0)	9.2 (7.5-10.0)	9.2 (7.2-10.0)	9.1 (7.2-10.0)	9.0 (7.3-10.0)	9.2 (7.5-10.0)	9.3 (7.2-10.0)	9.1 (7.2-10.0)
Nasal symptom VAS composite‡ score, median (range) (scale: 0-10)†	9.0 (7.9-10.0)	9.3 (7.5-10.0)	9.2 (6.0-10.0)	9.0 (4.9-10.0)	9.1 (6.0-10.0)	9.1 (6.9-10.0)	9.3 (6.4-10.0)	9.1 (4.9-10.0)
Loss of sense of smell VAS score, median (range) (scale: 0-10)†	9.7 (8.3-10.0)	9.9 (8.5-10.0)	10.0 (6.7-10.0)	10.0 (0.9-10.0)	10.0 (8.0-10.0)	9.9 (0.9-10.0)	10.0 (6.7-10.0)	10.0 (7.2-10.0)
SNOT-22 total score, median (range)†	65.0 (19-92)	62.0 (33-86)	64.0 (21-110)	65.0 (17-105)	64.0 (19-110)	60 (28-100)	64.5 (21-107)	66.0 (17-105)
Patients with asthma, n (%)	9 (56.3)	7 (35.0)	140 (75.7)	133 (71.5)	41 (66.1)	33 (49.3)	108 (77.7)	107 (77.0)
Patients with AERD, n (%)	3 (18.8)	5 (25.0)	60 (32.4)	40 (21.5)	17 (27.4)	10 (14.9)	46 (33.1)	35 (25.2)

BMI, Body mass index; *mepo*, mepolizumab 100 mg subcutaneous; *OCS*, oral corticosteroid.
*Twenty-five percent of patients in the ITT population had partial dates for previous surgeries. Where partial dates were available, missing day was assumed as the last day of the month and missing month as December.
†Higher scores indicate greater disease severity or worse quality of life.
‡Combining scores for nasal obstruction, nasal discharge, mucus in the throat, and loss of sense of smell.

characteristics regardless of blood eosinophil count; however, a higher proportion of patients with baseline blood eosinophil counts ≥150 cells/μL or ≥300 cells/μL had comorbid asthma or comorbid AERD compared with those who had baseline blood eosinophil counts <150 cells/μL or <300 cells/μL, respectively (Table II).

Coprimary end points

In the ITT population, more patients had greater than or equal to 1-point improvement from baseline in total endoscopic NP score at week 52 with mepolizumab (50.5%, n = 104 of 206) versus placebo (28.4%, n = 57 of 201; $P < .0001$).[24] This benefit of mepolizumab relative to placebo was observed across both comorbidities: comorbid asthma (52.9%, n = 74 of 140 vs 29.5%, n = 44 of 149) (Fig 1, *A*); comorbid AERD (51.1%, n = 23 of 45 vs 20.6%, n = 13 of 63) (Fig 1, *B*). Similar percentages of patients without these comorbidities also saw greater than or equal to 1-point improvement from baseline in total endoscopic NP score when treated with mepolizumab versus placebo (Fig 1, *A* and *B*). A similar trend was observed for patients with a greater than or equal to 2-point improvement from baseline in total endoscopic NP score at week 52 (Fig 1, *A* and *B*). For patients with a baseline blood eosinophil count of ≥150 cells/μL or ≥300 cells/μL, more patients had greater than or equal to 1-point improvement from baseline in total endoscopic NP score at week 52 with mepolizumab treatment versus placebo (49.5%, n = 92 of 186 vs 28.1%, n = 52 of 185 and 50.4%, n = 70 of 139 and 28.1%, n = 39 of 139, respectively; Fig 1, *C* and *D*); a similar trend was observed in patients with greater than or equal to 2-point improvement from baseline in total endoscopic NP score at week 52 (Fig 1, *C* and *D*). These outcomes were similar in patients with blood eosinophil counts <150 cells/μL and <300 cells/μL (Fig 1, *C* and *D*).

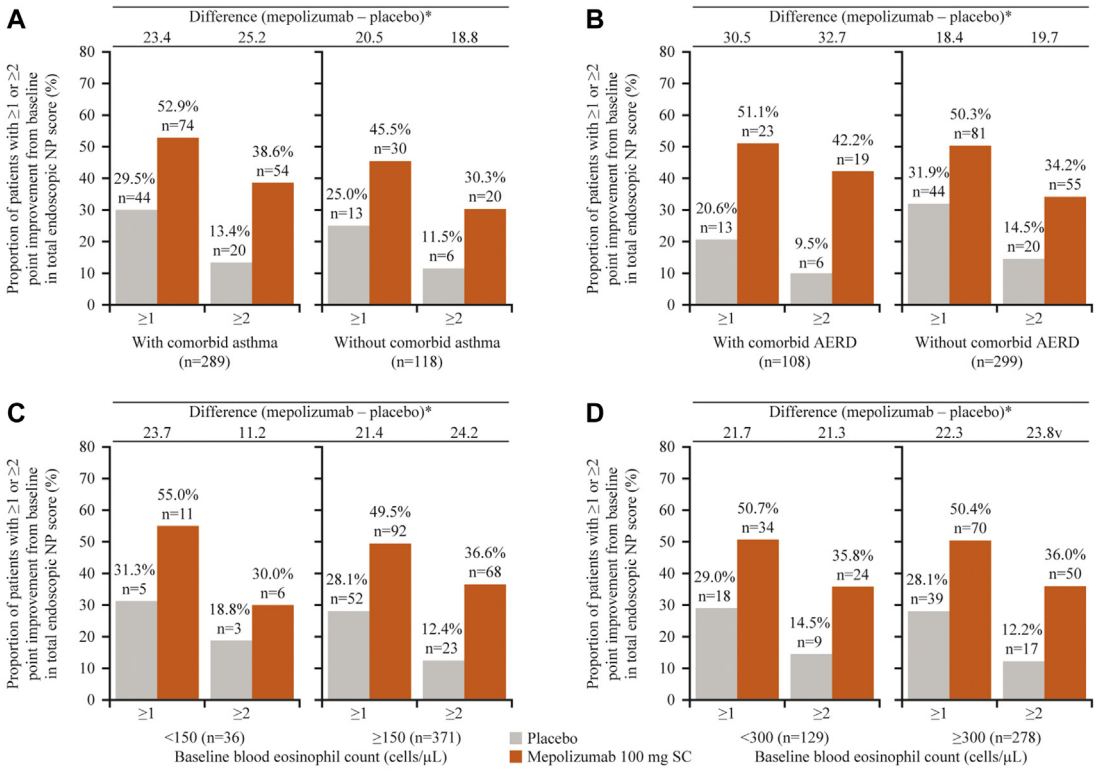

FIG 1. Proportion of patients with 1-point or more or 2-point or more improvement from baseline in total endoscopic NP score at week 52 for patients by (**A** and **B**) comorbidity and (**C** and **D**) baseline blood eosinophil count. *Difference in percentage between mepolizumab and placebo.

For nasal obstruction VAS score, more patients showed a more than 3-point improvement from baseline during weeks 49 to 52 with mepolizumab versus placebo (ITT: 60.2%, n = 124 of 206 vs 36.3%, n = 73 of 201; $P < .0001$).[24] Across both comorbidities, a higher proportion of patients treated with mepolizumab versus placebo had a more than 3-point improvement from baseline during weeks 49 to 52 (comorbid asthma: 60.0%, n = 84 of 140 vs 34.9%, n = 52 of 149, Fig 2, *A*; comorbid AERD: 64.4%, n = 29 of 45 vs 30.2%, n = 19 of 63, Fig 2, *B*). A similar trend was seen for patients treated with mepolizumab versus placebo without these comorbidities (Fig 2, *A* and *B*). For patients with a baseline blood eosinophil count ≥150 cells/μL or ≥300 cells/μL, a higher proportion of patients had a more than 3-point improvement from baseline in nasal obstruction VAS score during weeks 49 to 52 with mepolizumab versus placebo (≥150 cells/μL: 59.1%, n = 110 of 186 vs 34.1%, n = 63 of 185; ≥300 cells/μL: 59.0%, n = 82 of 139 and 32.4%, n = 45 of 139, respectively; Fig 2, *C* and *D*, respectively). A similar trend was seen in patients with baseline blood eosinophil counts <300 cells/μL (Fig 2, *D*); however, the difference in the proportion of patients who had a more than 3-point improvement from baseline in nasal obstruction VAS score during weeks 49 to 52 between the mepolizumab and placebo groups was less clear in those with baseline blood eosinophil counts <150 cells/μL (Fig 2, *C*).

Improvements in the coprimary end points with mepolizumab versus placebo were generally observed within the baseline blood eosinophil count categories: ≤300, >300 to ≤500, >500 to ≤700, and >700 cells/μL (see Figs E2 and E3 in this article's Online Repository at www.jacionline.org).

Secondary end points

Over the 52-week treatment period, patients receiving mepolizumab had a lower risk of surgery compared with those receiving placebo.[24] The reduction in risk of surgery with mepolizumab versus placebo was greater in patients without comorbid asthma than in those with comorbid asthma (Fig 3, *A*). Reductions in the risk of surgery with mepolizumab relative to placebo were similar for patients irrespective of the presence or absence of AERD. A greater decrease in risk of surgery with mepolizumab versus placebo over the 52-week treatment period was observed in patients with a baseline blood eosinophil count ≥150 cells/μL and ≥300 cells/μL than in those with baseline blood eosinophil counts <150 cells/μL and <300 cells/μL, respectively (Fig 3, *A*). Overall, there were fewer actual surgeries in patients treated with mepolizumab versus placebo in all subgroups (Fig 3, *A*).

Patients treated with mepolizumab had a lower probability of requiring SCS for NP up to week 52 versus placebo[24]; a similar trend was observed in patients with/without comorbid asthma or with/without comorbid AERD (Fig 3, *B*). For patients with a baseline blood eosinophil count ≥150 cells/μL or ≥300 cells/μL, there was a trend for a greater decrease in the need for SCS use for NP with mepolizumab versus placebo, compared with patients with baseline blood eosinophil counts <150 cells/μL and <300 cells/μL, respectively (Fig 3, *B*). Overall, a trend for a lower proportion of patients receiving 1 or more course of SCS for NP was observed with mepolizumab versus placebo treatment in all subgroups (Fig 3, *B*).

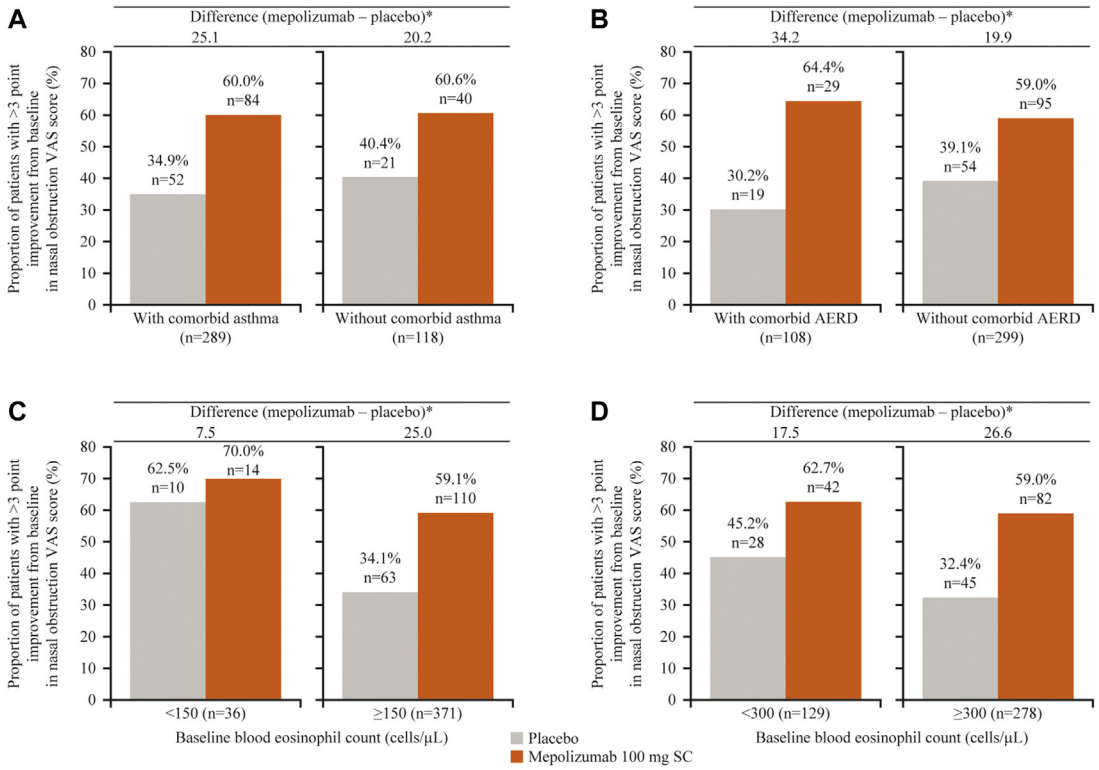

FIG 2. Proportion of patients with more than 3-point improvement from baseline in nasal obstruction VAS score during weeks 49 to 52 for patients by (**A** and **B**) comorbidity and (**C** and **D**) baseline blood eosinophil count. *Difference in percentage between mepolizumab and placebo.

Mepolizumab treatment was also associated with an improvement in overall VAS symptom score, SNOT-22 score, composite VAS score, and loss of smell VAS score versus placebo, for all patients with or without comorbid asthma or AERD (Fig 4). Mepolizumab, versus placebo, was associated with an increased proportion of patients with more than 3-point improvement in overall VAS symptom score, composite VAS score, and loss of smell VAS score in comorbid asthma and comorbid AERD subgroups as well as in subgroups without these comorbidities (see Table E1 in this article's Online Repository at www.jacionline.org). Likewise, for patients with a baseline blood eosinophil count ≥150 cells/μL, <300 cells/μL, or ≥300 cells/μL, mepolizumab treatment was associated with a trend for improvements in overall VAS symptom score, SNOT-22 total score, and composite VAS score versus placebo (Fig 4). For SNOT-22 score, the proportion of patients with a change in SNOT-22 score of 9 points or more from baseline by week 52 was higher with mepolizumab versus placebo for all subjects with or without comorbid asthma, or comorbid AERD, and in all baseline blood eosinophil count subgroups (see Table E2 in this article's Online Repository at www.jacionline.org).

Exacerbations and asthma control in patients with comorbid asthma

During the 52-week study period, 6 of 140 (4.3%) patients had 6 asthma exacerbations in the mepolizumab treatment group compared with 11 of 149 (7.4%) patients with 20 exacerbations in the placebo group. The annual rate of exacerbations (95% CI) was 0.05 with mepolizumab (0.02-0.12) versus 0.15 with placebo (0.08-0.26). The rate ratio (95% CI) was 0.33 (0.12-0.95).

At week 52, the mean ± SD ACQ-5 score was 1.19 ± 1.21 in patients with comorbid asthma treated with mepolizumab compared with 1.74 ± 1.42 with placebo. Mepolizumab compared with placebo resulted in a greater improvement in ACQ-5 scores from baseline in patients with comorbid asthma (difference [95% CI], -0.66 [-0.92 to -0.40]) at week 52. In addition, a higher proportion of patients with comorbid asthma experienced a change of 0.5 point or more in the ACQ-5 score (MCID) from baseline with mepolizumab versus placebo (56.5%, n = 78 of 138 vs 35.4%, n = 51 of 144, respectively; odds ratio [95% CI], 2.42 [1.43-4.11]).

Safety

The proportion of patients who experienced on-treatment AEs was similar for patients receiving mepolizumab versus placebo across all comorbidity and blood eosinophil count subgroups. The most frequently reported AEs were nasopharyngitis and headache (Tables III and IV).

DISCUSSION

These subgroup analyses of SYNAPSE demonstrate that mepolizumab 100 mg SC versus placebo reduced NP size, nasal obstruction, risk of surgery, and use of SCS for NP, while improving nasal symptoms in patients with severe, bilateral CRSwNP, regardless of the presence/absence of asthma or AERD. As mechanistically expected, there was an overall trend

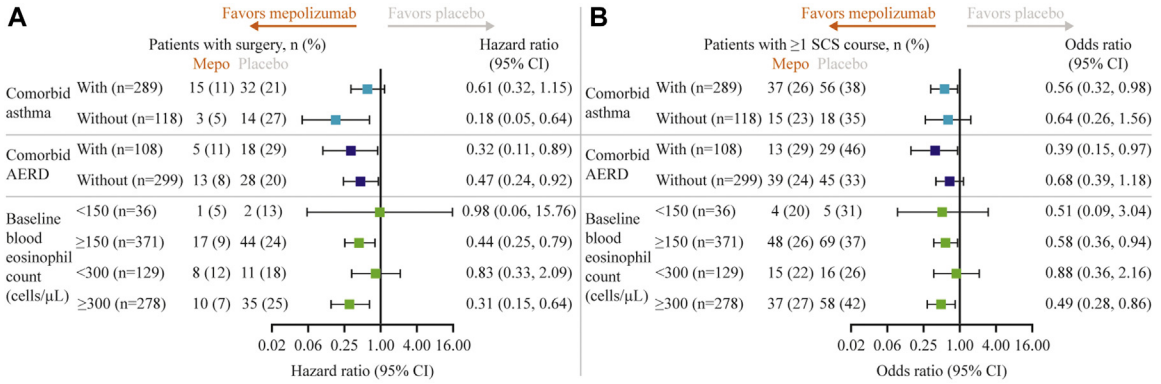

FIG 3. Risk of (**A**) surgery and (**B**) odds of patients requiring SCS for NP by week 52 for patients receiving mepolizumab or placebo with or without comorbid asthma, with or without comorbid AERD, and by baseline blood eosinophil count. *Mepo*, Mepolizumab.

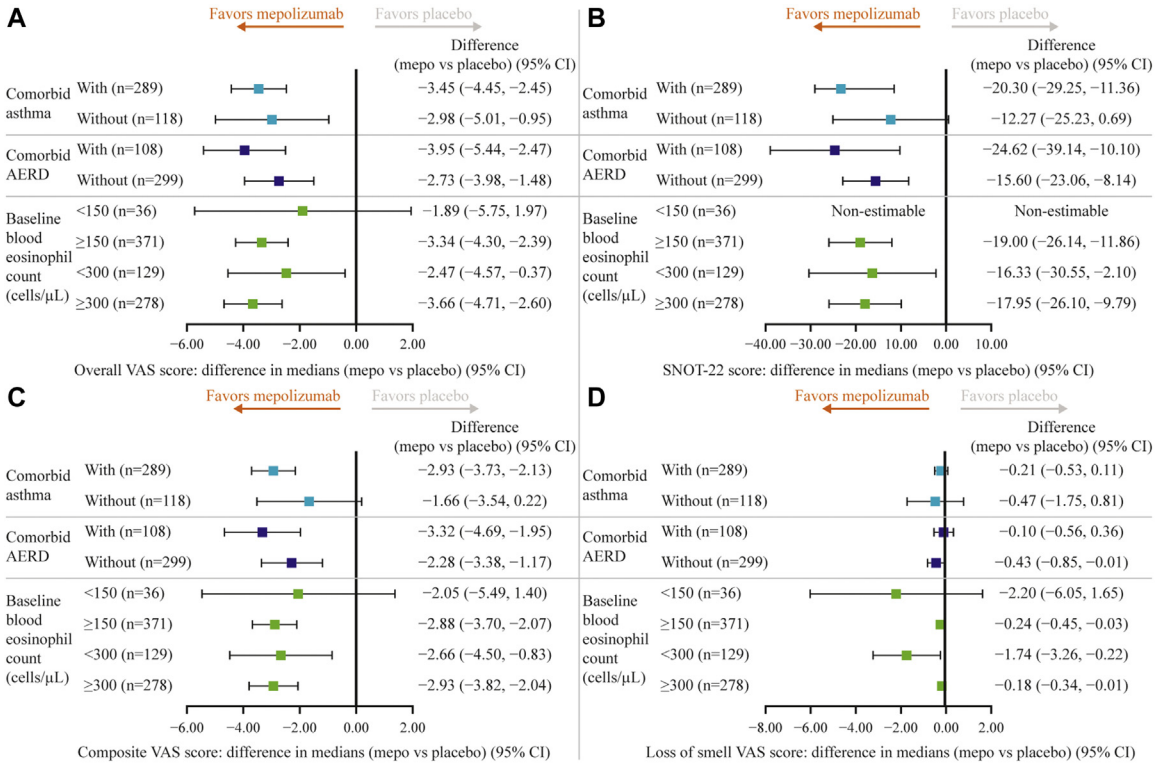

FIG 4. Change from baseline in overall VAS symptom score (**A**) by weeks 49 to 52, (**B**) SNOT-22 total score at week 52, (**C**) composite VAS score by weeks 49 to 52, and (**D**) loss of smell VAS score by weeks 49 to 52 for patients receiving mepolizumab or placebo by comorbidity and baseline blood eosinophil count. *Mepo*, Mepolizumab 100 mg subcutaneous.

for mepolizumab to provide greater benefit in patients with a baseline blood eosinophil count ≥150 cells/µL versus those with a baseline blood eosinophil count <150 cells/µL and in those with a count ≥300 cells/µL versus <300 cells/µL. Consistent with the primary SYNAPSE results,[24] these subgroup analyses support the use of mepolizumab in addition to SoC in patients with severe CRSwNP.

SYNAPSE targeted patients with severe and uncontrolled disease in accordance with the 2019 EUFOREA and 2020 European Position Paper on Rhinosinusitis and Nasal Polyps expert team definition.[3,18] As such, mepolizumab has already shown benefit to patients with severe CRSwNP,[24] and these analyses explored whether comorbidities impacted results from the overall SYNAPSE study population. Several studies have reported high disease burden in patients with uncontrolled disease irrespective of optimized SoC.[8,9,11,12] Despite the high disease burden in these patients, our data suggest that mepolizumab is efficacious in patients with or without these comorbidities, and the safety profiles are similar between the groups. Interestingly, our analyses of patients with severe CRSwNP and comorbid asthma show that exacerbation frequency and asthma control improved with mepolizumab versus placebo, indicating that

TABLE III. On-treatment safety profile for patients with or without comorbid asthma or with or without comorbid AERD

	Comorbid asthma				Comorbid AERD			
	With		Without		With		Without	
On-treatment safety profile	Placebo (n = 149)	Mepo (n = 140)	Placebo (n = 52)	Mepo (n = 66)	Placebo (n = 63)	Mepo (n = 45)	Placebo (n = 138)	Mepo (n = 161)
Any AE, n (%)*	128 (85.9)	114 (81.4)	42 (80.8)	55 (83.3)	57 (90.5)	42 (93.3)	113 (81.9)	127 (78.9)
AE related to study treatment, n (%)	14 (9.4)	20 (14.3)	5 (9.6)	10 (15.2)	8 (12.7)	11 (24.4)	11 (8.0)	19 (11.8)
Any SAE, n (%)*	14 (9.4)	3 (2.1)	0	9 (13.6)	7 (11.1)	3 (6.6)	7 (5.1)	9 (5.6)
Most common AE occurring in >10% of patients, n (%)								
Nasopharyngitis	38 (25.5)	32 (22.9)	8 (15.4)	20 (30.3)	14 (22.2)	18 (40.0)	32 (23.2)	34 (21.1)
Headache	34 (22.8)	29 (20.7)	10 (19.2)	8 (12.1)	19 (30.2)	16 (35.6)	25 (18.1)	21 (13.0)
Asthma	17 (11.4)	4 (2.9)	0	0	7 (11.1)	1 (2.2)	11 (8.0)	3 (1.9)
Sinusitis	16 (0.7)	6 (4.3)	6 (11.5)	4 (6.1)	7 (11.1)	0	15 (10.9)	10 (6.2)
Epistaxis	12 (8.1)	10 (7.1)	6 (11.5)	7 (10.6)	4 (6.3)	5 (11.1)	14 (10.1)	12 (7.5)
Acute sinusitis	7 (4.7)	9 (6.4)	6 (11.5)	4 (6.1)	4 (6.3)	1 (2.2)	9 (6.5)	12 (7.5)

mepo, Mepolizumab 100 mg subcutaneous; *SAE*, serious adverse event.
*Includes data up to week 52.

TABLE IV. On-treatment safety profile by baseline blood eosinophil count.

	Baseline blood eosinophil count (cells/μL)							
	<150		≥150		<300		≥300	
On-treatment safety profile	Placebo (n = 16)	Mepo (n = 20)	Placebo (n = 185)	Mepo (n = 186)	Placebo (n = 62)	Mepo (n = 67)	Placebo (n = 139)	Mepo (n = 139)
Any AE, n (%)*	14 (87.5)	17 (85.0)	156 (84.3)	152 (81.7)	52 (83.9)	58 (86.6)	118 (84.9)	111 (79.9)
AE related to study treatment, n (%)	0	3 (15.0)	19 (10.3)	27 (14.5)	2 (3.2)	7 (10.4)	17 (12.2)	23 (16.5)
Any SAE, n (%)*	1 (6.3)	2 (10.0)	13 (7.0)	10 (5.4)	3 (4.8)	6 (9.0)	11 (7.9)	6 (4.3)
Most common AE occurring in >10% of patients, n (%)								
Nasopharyngitis	2 (12.5)	3 (15.0)	44 (23.8)	49 (26.3)	13 (21.0)	15 (22.4)	33 (23.7)	37 (26.6)
Headache	3 (18.8)	3 (15.0)	41 (22.2)	34 (18.3)	12 (19.4)	10 (14.9)	32 (23.0)	27 (19.4)
Sinusitis	2 (12.5)	3 (15.0)	20 (10.8)	7 (3.8)	7 (11.3)	6 (9.0)	15 (10.8)	4 (2.9)
Acute sinusitis	2 (12.5)	2 (10.0)	11 (5.9)	11 (5.9)	5 (8.1)	7 (10.4)	8 (5.8)	6 (4.3)
Epistaxis	0 (0)	3 (15.0)	18 (9.7)	14 (7.5)	5 (8.1)	8 (11.9)	13 (9.4)	9 (6.5)
NP	3 (18.8)	0 (0)	13 (7.0)	8 (4.3)	4 (6.5)	2 (3.0)	12 (8.6)	6 (4.3)
Chronic sinusitis	2 (12.5)	0 (0)	0 (0)	0 (0)	2 (3.2)	1 (1.5)	0 (0)	0 (0)
Upper respiratory tract infection	2 (12.5)	0 (0)	12 (6.5)	12 (6.5)	4 (6.5)	3 (4.5)	10 (7.2)	9 (6.5)

mepo, Mepolizumab 100 mg subcutaneous; *SAE*, serious adverse event.
*Includes data up to week 52.

mepolizumab is of benefit to both upper and lower airway asthma symptoms in these patients. These data are consistent with both clinical and real-world studies assessing efficacy of mepolizumab 100 mg SC in patients with severe eosinophilic asthma.[20,30,31]

In line with the primary analysis of SYNAPSE,[24] we report that fewer patients receiving mepolizumab underwent actual nasal surgery versus those receiving placebo, regardless of asthma or AERD status. The benefit of mepolizumab in reducing nasal surgery aligns with the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 recommendations to reduce surgery.[3] The benefit of mepolizumab in reducing actual surgery may be an important consideration for patients expressing concerns over the risks associated with, and the disruptive nature of, surgery.[32] Notably, patients without comorbid asthma had a greater reduction in risk of nasal surgery than those with comorbid asthma. Patients without versus with comorbid asthma had lower baseline blood eosinophil counts, which have been shown to correlate with better disease control,[33] thereby potentially reducing the need for further surgery in patients without comorbid asthma. As short courses of SCS were permitted as part of SoC in SYNAPSE, a higher number of patients with comorbid asthma receiving placebo were prescribed 1 or more course of SCS than patients receiving mepolizumab. Thus, patients with comorbid asthma in the placebo group may have experienced some improvements in NP symptoms due to receiving SCS for their asthma symptoms, potentially disproportionally reducing the need for surgery in the placebo population. Further disparity between the mepolizumab and placebo treatment groups for patients with comorbid asthma may be due to the SCS-sparing effect of mepolizumab in patients with asthma.[34] Consistent with the SCS-sparing effect of mepolizumab,[34] we also report that fewer patients required SCS with mepolizumab versus placebo, irrespective of comorbid asthma, comorbid AERD, or baseline blood eosinophil count. Despite the efficacy of mepolizumab in patients with comorbid AERD, we are not inferring tolerance to nonsteroidal anti-inflammatory drugs in clinical practice.

Our phase III data suggest that mepolizumab was efficacious and is a treatment option for patients with severe CRSwNP irrespective of blood eosinophil count; a follow-up evaluation of treatment response at 6 months is recommended as per EUFOREA recommendations for biologic use.[35] Although eosinophil tissue infiltration and markers of type 2 inflammation are often associated with CRSwNP, the underlying mechanisms that contribute to disease pathology are not fully understood.[1,3,36] As such, our data confirm that eosinophils are an appropriate and effective target in severe CRSwNP.

The limitations of the study design have been reported.[24] The current exploratory analyses relate to the presence of comorbid asthma and comorbid AERD being determined from patient medical history, with no further diagnoses for these diseases being performed during the study. This may have resulted in misdiagnoses of those without a comorbidity. In addition, low patient numbers in the <150 cells/μL subgroup may have obscured the benefits of mepolizumab in patients with blood eosinophil counts

<150 cells/μL. The low patient numbers were likely due to the inclusion criteria, because patients with severe CRSwNP are more likely to have higher blood eosinophil counts than those with less severe disease. Finally, although blood eosinophil count is an accessible, measurable marker in patients with severe CRSwNP, other biomarkers of nasal polyposis (not assessed in this study) may also exist. The low patient numbers also prevent any meaningful analysis assessing the effectiveness of mepolizumab in patients with blood eosinophil counts <150 cells/μL who do not have either comorbid disease. Therefore, further studies in this population are warranted.

These exploratory analyses indicate that mepolizumab is efficacious for the treatment of severe CRSwNP, irrespective of the presence or absence of comorbid asthma or comorbid AERD. Our data showed a trend for greater clinical benefit in patients with baseline blood eosinophil counts ≥150 cells/μL versus <150 cells/μL and in those with baseline blood eosinophil counts ≥300 cells/μL versus <300 cells/μL. This provides further evidence that baseline blood eosinophil counts ≥150 cells/μL or ≥300 cells/μL may be suitable biomarkers for responsiveness to mepolizumab in patients with severe CRSwNP and supports the previously described relationship between mepolizumab and baseline blood eosinophil count in severe eosinophil asthma.[19]

Clinical implications: Mepolizumab should be considered for the treatment of CRSwNP, particularly in patients with comorbid asthma or AERD.

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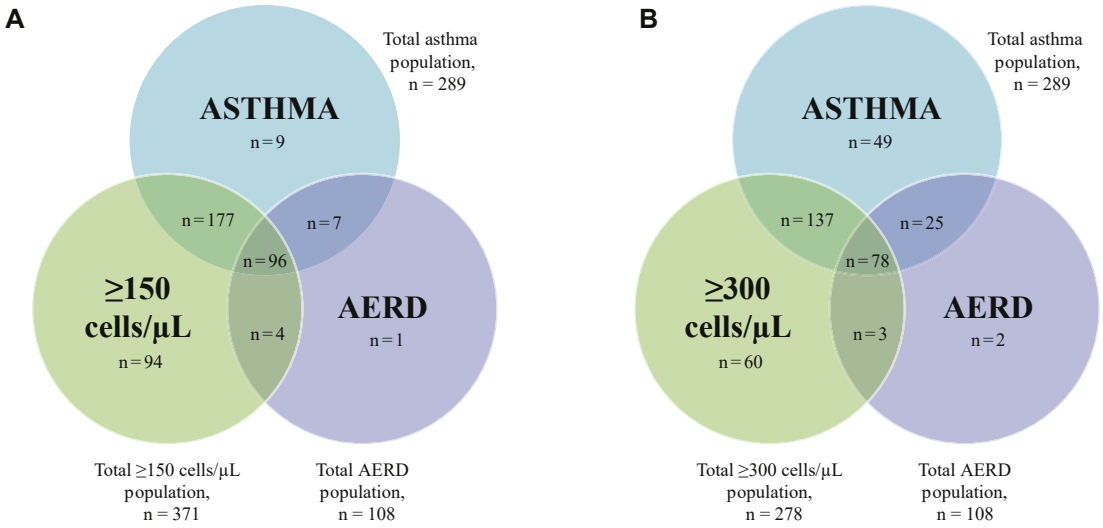

FIG E1. Proportion of patients with comorbid asthma, comorbid AERD, and blood eosinophil count (**A**) ≥150 cells/μL and (**B**) ≥300 cells/μL.

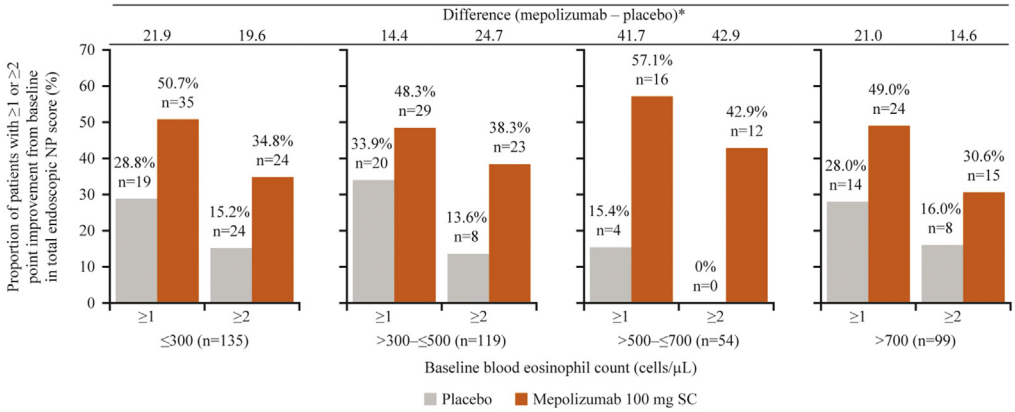

FIG E2. Proportion of patients with greater than or equal to 1- or greater than or equal to 2-point improvement from baseline in total endoscopic NP score at week 52 by baseline blood eosinophil count thresholds. *Difference in percentage points between mepolizumab and placebo.

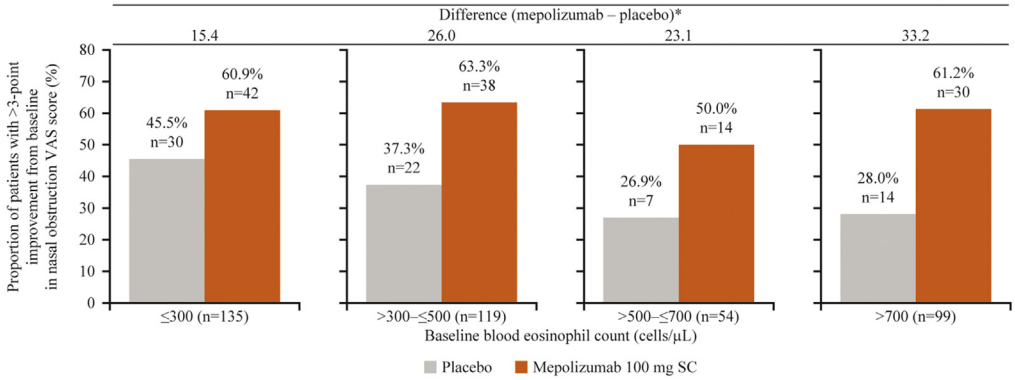

FIG E3. Proportion of patients with more than 3-point improvement from baseline in nasal obstruction VAS score during weeks 49 to 52 by baseline blood eosinophil count thresholds. *Difference in percentage between mepolizumab and placebo.

TABLE E1. Proportion of patients with >3-point improvement in overall VAS symptom score, composite VAS score, and loss of smell VAS score by weeks 49 to 52 for patients with or without comorbid asthma, with or without comorbid AERD, and by baseline blood eosinophil count

>3-point improvement from baseline at weeks 49 to 52	Comorbid asthma		Comorbid AERD		Baseline blood eosinophil count (cells/μL)			
	With (n = 289)	Without (n = 118)	With (n = 108)	Without (n = 299)	<150 (n = 36)	≥150 (n = 371)	<300 (n = 129)	≥300 (n = 278)
Overall VAS symptom score								
Placebo, n (%)	54 of 149 (36.2)	22 of 52 (42.3)	19 of 63 (30.2)	57 of 138 (41.3)	10 of 16 (62.5)	66 of 185 (35.7)	36 of 62 (58.1)	47 of 139 (33.8)
Mepolizumab 100 mg SC, n (%)	86 of 140 (61.4)	41 of 66 (62.1)	30 of 45 (66.7)	97 of 161 (60.2)	14 of 20 (70.0)	113 of 186 (60.8)	50 of 67 (74.6)	82 of 139 (59.0)
Composite VAS score								
Placebo, n (%)	49 of 149 (32.9)	23 of 52 (44.2)	28 of 63 (44.4)	54 of 138 (39)	10 of 16 (62.5)	62 of 185 (33.5)	25 of 62 (40.3)	47 of 139 (33.8)
Mepolizumab 100 mg SC, n (%)	82 of 140 (58.6)	39 of 66 (59.1)	28 of 45 (62.2)	91 of 161 (57)	14 of 20 (70.0)	105 of 186 (56.5)	40 of 67 (59.7)	79 of 139 (56.8)
Loss of sense of smell VAS score								
Placebo, n (%)	24 of 149 (16.1)	15 of 52 (28.8)	6 of 63 (9.5)	33 of 138 (23.9)	9 of 16 (56.3)	30 of 185 (16.2)	15 of 62 (24.2)	24 of 139 (17.3)
Mepolizumab 100 mg SC, n (%)	49 of 140 (35.0)	25 of 66 (37.9)	16 of 45 (35.0)	58 of 161 (36.0)	11 of 20 (55.0)	63 of 186 (33.9)	28 of 67 (41.8)	46 of 139 (33.1)

TABLE E2. Proportion of patients with a ≥9-point improvement from baseline in SNOT-22 score by week 52 in patients receiving mepolizumab or placebo treatment with or without comorbid asthma, with or without comorbid AERD, and by baseline blood eosinophil count

	Comorbid asthma		Comorbid AERD		Baseline blood eosinophil count (cells/μL)			
≥9-point improvement in SNOT-22 score from baseline by week 52	**With (n = 289)**	**Without (n = 118)**	**With (n = 108)**	**Without (n = 299)**	**<150 (n = 36)**	**≥150 (n = 371)**	**<300 (n = 129)**	**≥300 (n = 278)**
Placebo, n of N (%)	78 of 149 (52.3)	28 of 52 (53.8)	31 of 63 (49.2)	75 of 138 (54.3)	10 of 16 (62.5)	96 of 185 (51.9)	36 of 62 (58.1)	70 of 139 (50.4)
Mepolizumab 100 mg SC, n of N (%)	101 of 140 (72.1)	49 of 66 (74.2)	32 of 45 (71.1)	118 of 161 (73.3)	16 of 20 (80.0)	134 of 186 (72.0)	50 of 67 (74.6)	100 of 139 (71.9)

SNOT-22 scores ranged from 0 to 110. A change from baseline in SNOT-22 score by week 52 of ≥9.0-point improvement is shown; >8.9 points is reported as an MCID.[E1]