

Mepolizumab Reduces Systemic Corticosteroid Use in Chronic Rhinosinusitis With Nasal Polyps



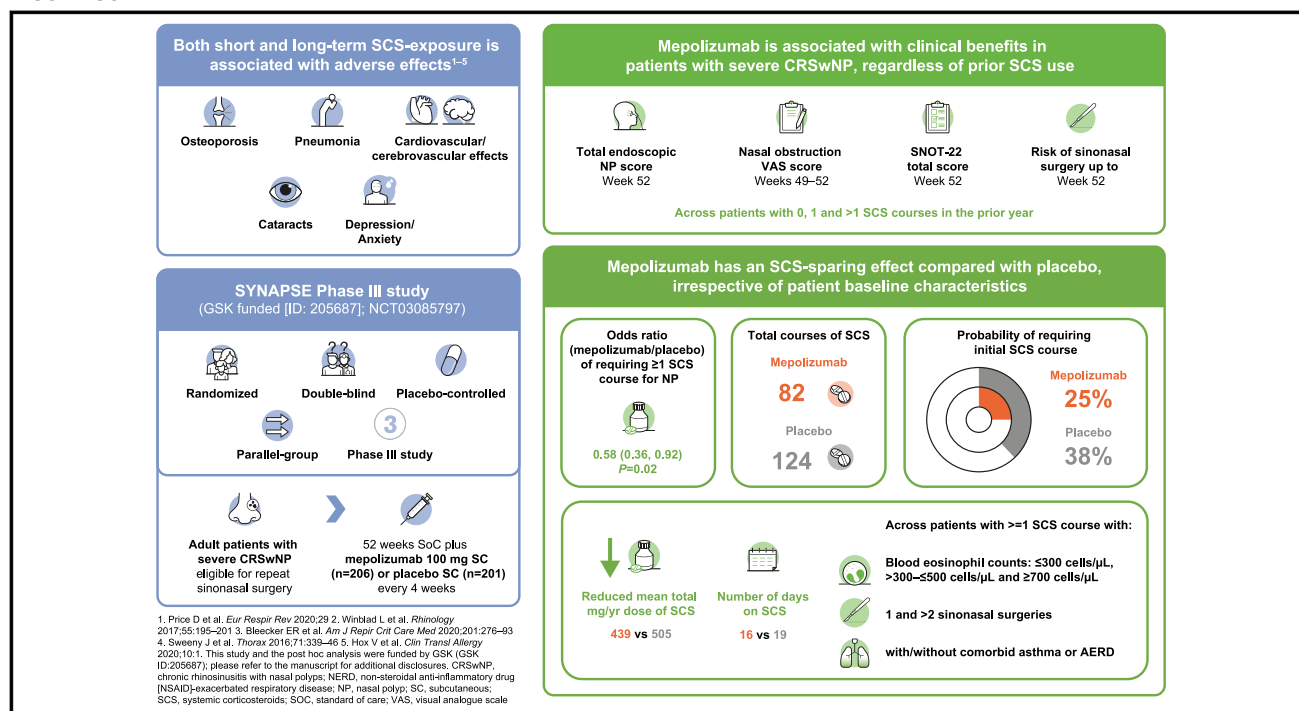
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What is already known about this topic? In the phase III SYNAPSE trial, mepolizumab versus placebo significantly reduced nasal polyp size and sinonasal symptoms, sinus surgery occurrence, and systemic corticosteroid (SCS) use in patients with severe chronic rhinosinusitis with nasal polyps.

What does this article add to our knowledge? This article demonstrates that mepolizumab versus placebo is associated with improved treatment responses irrespective of prior SCS use, and SCS-sparing capabilities, overall and in patients with differing clinical characteristics.

How does this study impact current management guidelines? Given the adverse effects associated with SCS use, mepolizumab could be used to reduce reliance on SCSs and the associated adverse effect burden of SCSs in patients with recurrent, refractory, severe chronic rhinosinusitis with nasal polyps.

VISUAL SUMMARY



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Abbreviations used

CRSwNP- chronic rhinosinusitis with nasal polyps
NP- nasal polyp
OCS- oral corticosteroid
SCS- systemic corticosteroid
SNOT-22- 22-item Sino-Nasal Outcome Test
VAS- visual analog scale

BACKGROUND: Systemic corticosteroids (SCSs) are associated with short- and long-term adverse effects.

OBJECTIVE: To assess mepolizumab efficacy according to prior SCS use and characterize mepolizumab's SCS-sparing capabilities, in patients with severe chronic rhinosinusitis with nasal polyps.

METHODS: In the randomized, double-blind, phase III SYNAPSE trial (NCT03085797), adults with severe chronic rhinosinusitis with nasal polyps eligible for repeat sinus surgery despite standard of care treatment received mepolizumab (100 mg subcutaneously) or placebo every 4 weeks for 52 weeks. The impact of prior SCS courses (0/1/>1) on mepolizumab versus placebo treatment responses (changes from baseline in total endoscopic nasal polyp [week 52], nasal obstruction visual analog scale [weeks 49-52], and 22-item Sino-Nasal Outcome Test total [week 52] scores) was analyzed *post hoc*. To characterize mepolizumab's SCS-sparing capabilities, time-to-first SCS course for nasal polyps (prespecified) and total prednisolone-equivalent oral corticosteroid dose by patient baseline characteristics (*post hoc*, in patients with ≥ 1 SCS course during SYNAPSE) were assessed up to week 52.

RESULTS: Mepolizumab versus placebo improved treatment responses, irrespective of prior SCS use. By week 52, the probability of requiring SCSs for nasal polyps (Kaplan-Meier

estimate [95% CI]) was lower with mepolizumab (25.4% [20.0-32.1]) versus placebo (37.5% [31.1-44.6]). In patients requiring 1 or more dose of SCSs, total (mean \pm SD mg/y) prednisolone-equivalent oral corticosteroid dose was lower with mepolizumab (438.9 ± 350.40) versus placebo (505.2 ± 455.091), overall and irrespective of prior sinus surgeries, blood eosinophil count, or comorbidities.

CONCLUSIONS: Mepolizumab is associated with clinical benefits in patients with severe chronic rhinosinusitis with nasal polyps regardless of prior SCS use and has an SCS-sparing effect. © 2023 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). (J Allergy Clin Immunol Pract 2023;11:3504-12)

Key words: Asthma; Mepolizumab; AERD; Aspirin-exacerbated respiratory disease; Refractory disease; Severe chronic rhinosinusitis with nasal polyps; Subgroup analysis; Systemic corticosteroids

INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a subtype of CRS characterized by inflammation of the nose and paranasal sinuses.^{1,2} Type 2, predominantly eosinophilic inflammation is a common feature of CRSwNP, with other immunologic subtypes often present.^{3,4} For patients, CRSwNP is often severe in nature and has a substantial negative impact on sleep^{5,6} along with health-related quality-of-life impairments similar to those of other chronic diseases such as diabetes, chronic obstructive pulmonary disease, and asthma.⁷⁻⁹

For patients with uncontrolled severe disease despite treatment with nasal lavage and intranasal corticosteroids, the standard treatment approach is administration of single or recurrent

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This study was funded by GSK (GSK ID: 205687; NCT03085797).

Conflicts of interest: G. Chupp has received advisory board fees, speaking fees, and research grants from GSK, AstraZeneca, Genentech, Sanofi Genzyme, Regeneron, Teva, and Novartis. I. Albid has received advisory board fees and consultation fees from Maylan, Menarini, GSK, MSD, Novartis, Sanofi, and Roche. N. L. Lugogo reports receiving non-speaker fees from Amgen, AstraZeneca, Avillion, Genentech, GSK, Novartis, Regeneron, Sanofi, Teva; honoraria for nonspeaker bureau presentations from GSK and AstraZeneca; and travel support from AstraZeneca; her institution has received research support from Amgen, AstraZeneca, Avillion, Evidera, Gossamer Bio, Genentech, GSK, Regeneron, Sanofi, Novartis, and Teva; and she is an honorary faculty member of the Observational and Pragmatic Research Institute but does not receive compensation for this role. H. H. Kariyawasam has received speaker fees and conference attendance support from GSK. A. Bourdin has received research grants and consulting fees from AstraZeneca-MedImmune, Boehringer Ingelheim, Cephalon/Teva, GSK, Novartis, and Sanofi-Regeneron; consulting fees from Med-in-Cell, Actelion, Merck, Roche, and Chiesi; and is an investigator/coinvestigator for trials promoted by AstraZeneca-MedImmune, Boehringer Ingelheim, GSK, Novartis, Sanofi/Regeneron, Chiesi, Actelion, Merck, Roche, Vertex, and Galapagos. A. M. Chaker has received research grants via Technical University Munich from Allegro Pharma, ALK-Abelló, AstraZeneca, Bencard/Allergen Therapeutics, ASIT Biotech, GSK,

Novartis, LETI, Roche, Zeller, Federal German Ministry of Education and Research, and the European Institute of Technology; advisory board/speaker fees via Technical University Munich from Allegro Pharma, ALK-Abelló, AstraZeneca, Bencard/Allergen Therapeutics, GSK, Immunotech, Lofarma, Novartis, LETI, Sanofi Genzyme/Regeneron, and Zeller; is a Board Member for the European Academy of Allergy and Clinical Immunology, European Forum of Research and Education in Allergy and Airway Disease, and German Society of Allergy and Clinical Immunology; and is also Scientific Advisor for the German Society of Applied Allergy, and former Chair of the German Society of Otorhinolaryngology and Head and Neck Surgery. S. G. Smith, A. R. Sousa, B. Mayer, and R. H. Chan are employees of GSK and own stocks/shares. A. Matucci has received speaker's honoraria from AstraZeneca, Novartis, and GSK, and honoraria for attending advisory panels with Sanofi, AstraZeneca, GSK, Novartis, and Chiesi.

Data sharing statement: GSK makes available anonymized individual participant data and associated documents from interventional clinical studies that evaluate medicines, on approval of proposals submitted to <https://www.gsk-studyregister.com/en/>.

Received for publication March 8, 2023; revised July 28, 2023; accepted for publication August 6, 2023.

Available online August 14, 2023.

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courses of systemic corticosteroids (SCSs).¹⁰ However, SCS use has several limitations. For example, both short- and long-term SCS exposure is associated with adverse effects including osteoporosis, pneumonia, cardiovascular/cerebrovascular effects, cataract, and depression/anxiety,¹¹⁻¹⁵ the management of which can result in a substantial economic burden.¹⁶ A cumulative exposure of 500 mg to less than 1000 mg SCSs is also associated with an increased risk for adverse effects compared with exposures of more than 0 mg to less than 500 mg.¹⁷ Furthermore, some patients with CRSwNP fail to achieve adequate disease control with SCSs.^{8,18} For these patients, sinus surgery may be indicated¹⁰; however, the long-term recurrence rate following sinus surgery is high, particularly in patients with eosinophil-rich endotypes.^{19,20} In 2 studies of patients with CRSwNP who had undergone sinus surgery, disease recurrence was reported in 79% and 82% of patients within 12 years of follow-up.^{19,21} Given the substantial burden associated with SCS use, biologic therapies directly or indirectly targeting eosinophils have the potential to reduce SCS use in dependent patients, as has been demonstrated in other eosinophilic diseases.²²⁻²⁶

Mepolizumab is a humanized monoclonal antibodies that targets IL-5, thereby blocking the proliferation, differentiation, activation, and survival of eosinophils.²⁷ Mepolizumab is associated with a range of clinical benefits in a number of eosinophilic diseases, including a reduced risk of exacerbations, improvement in symptom control and health-related quality of life, as well as having an SCS-sparing effect in severe eosinophilic asthma; increased time in remission and higher proportions of patients with remission in eosinophilic granulomatosis with polyangiitis; and a reduced occurrence of flares in hypereosinophilic syndrome.^{22,26,28-31} In the landmark randomized, placebo-controlled, phase III SYNAPSE trial, mepolizumab significantly improved nasal polyp (NP) size (total endoscopic NP score) and nasal obstruction (nasal obstruction visual analog scale [VAS] score¹⁰) compared with placebo in patients with recurrent, refractory CRSwNP in need of repeat surgery, as well as significantly reducing the occurrence of sinus surgery and the use of SCSs, and improving health-related quality of life as assessed with the 22-item Sino-Nasal Outcome Test (SNOT-22).³² As a result, mepolizumab is now approved for the treatment of severe eosinophilic asthma, CRSwNP, eosinophilic granulomatosis with polyangiitis, and hypereosinophilic syndrome in multiple regions worldwide.³³⁻³⁵ The objective of this analysis was to explore the relationship between prior SCS use and treatment response, and to characterize the SCS-sparing effect of mepolizumab in patients with CRSwNP.

METHODS

Study design

Full details of the SYNAPSE study have been described previously.³² In brief, SYNAPSE was a phase III randomized, double-blind, placebo-controlled, parallel-group, multicenter trial (GSK ID: 205687; NCT03085797). Patients were randomized (1:1) to receive mepolizumab 100 mg or placebo subcutaneously every 4 weeks, for 52 weeks, in addition to standard of care (daily mometasone furoate nasal spray and, if required, saline nasal lavage, and short courses of high-dose SCSs and/or antibiotics). The use of SCSs was based on the treating physician's assessment of clinical need and driven by clinical guidance. Patients maintained standard of care throughout the study period, and SCS rescue medication use was permitted at any time during the study.

The trial was conducted in accordance with the 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/>.

Patients

Full inclusion and exclusion criteria have been published previously.³² Eligible patients were 18 years or older with recurrent, refractory, severe bilateral NPs (defined as nasal obstruction VAS symptom score of more than 5 [maximum 10]) who were eligible for repeat surgery, as evidenced by an overall VAS symptom score of more than 7 (maximum 10) and endoscopic bilateral NP score of 5 or more (maximum 8), with a score of 2 or more in each nasal cavity, despite standard of care treatment. Patients had to have 1 or more sinus surgery (defined as any incision of the paranasal sinuses and removal of polyp tissue from the nasal cavity [polypectomy] and the sinuses) in the previous 10 years. In addition, patients had received stable maintenance therapy with intranasal spray (mometasone furoate) for 8 weeks or more before screening and displayed 2 or more different sinonasal symptoms for 12 weeks or more before screening (nasal blockage, obstruction or congestion, and/or nasal discharge [anterior or posterior nasal drip], with 1 or more of the following: nasal discharge, facial pain or pressure, and/or a reduction in or loss of smell). CS use was not permitted in the 4 weeks before screening. Patients were not eligible for randomization if there were changes in their CRSwNP maintenance therapy during the run-in period, including changes in or addition of an intranasal corticosteroid, a short-burst course of an SCS, a leukotriene receptor antagonist, or allergen immunotherapy. Only short courses of SCSs were permitted during the study. Patients were excluded if they had received biologic or immunosuppressive treatment within 5 terminal phase half-lives of screening.

End points and assessments

To assess the impact of prior SCS use on treatment response and the need for surgery, changes from baseline in total endoscopic NP score at week 52, nasal obstruction VAS score at weeks 49 to 52, SNOT-22 total score at week 52, and time-to-first sinus surgery up to week 52 were analyzed *post hoc* by the number of SCS courses in the year before enrollment (0, 1, >1).

To assess the SCS-sparing effect of mepolizumab, prespecified end points relating to SCS use during the study included the proportion of patients requiring 1 or more course of SCSs for NPs, the total number of SCS courses for NPs, and time-to-first SCS course for NPs, all up to week 52 in the intent-to-treat population. Among patients with 1 or more SCS course during the study, end points included the total dose (mg/y) of prednisolone-equivalent oral corticosteroid (OCS) for NPs (*post hoc* analysis), the proportion of patients receiving distinct dose categories of prednisolone-equivalent OCSs for NPs (prespecified analysis; categories: >0-100 mg/y, >100-200 mg/y, >200-300 mg/y, >300-400 mg/y, >400-500 mg/y, >500-600 mg/y, and >600 mg/y) and the total number of days on SCSs for NPs (prespecified analysis), all up to week 52.

To assess the potential impact of patient clinical characteristics on the SCS-sparing effect of mepolizumab, prespecified analyses included the proportion of patients requiring SCSs for NPs up to week 52 by the number of prior sinus surgeries (1, 2, >2), blood

eosinophil count (≤ 300 , ≥ 300 – ≤ 500 , > 500 – ≤ 700 , > 700 cells/ μL), comorbid asthma (yes, no), and comorbid AERD (yes, no). *Post hoc* analyses included total dose (mg/y) of prednisone-equivalent OCSs for NPs up to week 52 by the number of prior sinus surgeries (1, 2, > 2), blood eosinophil count (< 150 cells/ μL , ≥ 150 cells/ μL , < 300 cells/ μL , ≥ 300 cells/ μL ; different thresholds used vs prespecified analyses, owing to small patient numbers), comorbid asthma (yes, no), and comorbid AERD (yes, no). Safety data during SYNAPSE have been previously published.³²

Sample size and statistical analysis

All data reported up to week 52 were included in the analysis, regardless of treatment discontinuation. Sample size calculations and the hierarchical testing of secondary end points have been described previously.³² For the purposes of this study, courses of SCSs less than 7 days apart were considered as 1 course. Within a subgroup, total endoscopic NP score, nasal obstruction VAS score, SNOT-22 total score, and estimates of the treatment effect accounting for covariates of treatment group, geographical region, baseline score, and \log_e baseline blood eosinophil count (if applicable) were presented as a difference in medians based on a quantile regression model.^{36,37} Within a subgroup, the proportion of patients requiring SCSs for NPs was analyzed using a logistic regression model with covariates of treatment group, baseline NP score (centrally read), baseline nasal obstruction VAS score, \log_e baseline blood eosinophil count (if applicable), number of SCS courses in the previous 12 months (0, 1, > 1 ; ordinal), and geographic region. Time-to-first SCS course was determined using Kaplan-Meier estimates. All data were analyzed using SAS v 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Patient population

A total of 407 patients were included in the SYNAPSE intent-to-treat population; 206 received mepolizumab and 201 received placebo. The demographic and clinical characteristics of these patients have been previously reported.³² In the year before the study, 52% ($n = 210$) of patients had not received a course of SCSs for NPs, with 27% ($n = 111$) receiving 1 course and 21% ($n = 86$) more than 1 course.

Treatment response by prior SCS use

Improvements in total endoscopic NP score at week 52, nasal obstruction VAS score at weeks 49 to 52, and SNOT-22 total score at week 52 with mepolizumab versus placebo were largest in the subgroup of patients with 1 SCS course in the year before the study (Table I; see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The proportion of patients requiring sinus surgery up to week 52 was consistently lower with mepolizumab than with placebo across all baseline SCS use subgroups, with the largest benefit in patients with more than 1 SCS course in the year before the study (Table I).

SCS-sparing effect of mepolizumab

As previously reported, the proportion of patients requiring 1 or more course of SCSs for NPs during the study was lower with mepolizumab ($n = 52$ of 206 [25%]) versus placebo ($n = 74$ of 201 [37%]).³² Mepolizumab significantly reduced the odds of patients requiring 1 or more SCS course for NPs (odds ratio, 0.58; 95% CI, 0.36–0.92; $P = .02$), with mepolizumab-treated patients receiving a total of 82 courses compared with a total of 124 courses in the placebo group.³²

Figure 1 shows the time-to-first course of SCSs for NPs over the 52-week treatment period; the probability of requiring an initial course of SCSs for NPs by week 52 was lower in the mepolizumab group (25.4%; 95% CI, 20.0–32.1) than in the placebo group (37.5%; 95% CI, 31.1–44.6).

Among patients with 1 or more SCS course for NPs during the study, mepolizumab treatment reduced the mean \pm SD total prednisolone-equivalent OCS dose for NPs (438.9 ± 350.4 mg/y) versus placebo (505.2 ± 455.1 mg/y). Furthermore, smaller proportions of patients treated with mepolizumab versus placebo received more than 200 mg/y (Figure 2), and more than 200 to 300 mg/y and more than 400 to 500 mg/y of prednisolone-equivalent OCSs for NPs (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Patients receiving mepolizumab spent a similar number of days on SCSs to those receiving placebo (mean \pm SD, 15.7 ± 11.9 vs 19.0 ± 18.5 days). One patient receiving mepolizumab with reported SCS use for 335 days was considered an outlier and was excluded from this analysis, because all other mepolizumab-treated patients had used SCSs for 51 days or less.

Impact of baseline characteristics on the SCS-sparing effect of mepolizumab

The proportion of patients receiving 1 or more SCS course during the 52-week study period was lower with mepolizumab than with placebo in patients with blood eosinophil counts less than or equal to 300 cells/ μL , more than 300 to less than or equal to 500, and more than or equal to 700 cells/ μL , in patients with 1 or more than 2 previous surgeries, and in patients with or without comorbid asthma and in patients with or without comorbid AERD (Figure 3). The total prednisolone-equivalent OCS dose during the study was reduced with mepolizumab versus placebo in patients with 1 or more than 2 previous surgeries and baseline blood eosinophil counts of less than 150 cells/ μL , more than or equal to 150 cells/ μL , and more than or equal to 300 cells/ μL , and in patients with and without comorbid asthma and comorbid AERD (Table II).

DISCUSSION

The phase III SYNAPSE study demonstrated the efficacy and safety of mepolizumab versus placebo among patients with recurrent, refractory, severe, bilateral CRSwNP eligible for repeat surgery.³² SYNAPSE patients receiving mepolizumab experienced a range of clinical benefits including reduced polyp size, improved nasal obstruction, and a reduced need for sinus surgery and SCSs.³² This analysis demonstrated that clinical improvements were consistently observed with mepolizumab versus placebo in SYNAPSE patients, irrespective of baseline SCS use. In addition, the reduction in SCS use previously shown with mepolizumab during SYNAPSE was further characterized; mepolizumab versus placebo treatment was associated with a reduced probability of requiring SCSs for NPs during the study. In patients with 1 or more SCS course, the prednisolone-equivalent OCS dose was also reduced with mepolizumab versus placebo treatment. These data also show consistent reductions in SCS use across patients with varying clinical characteristics, including differing numbers of previous surgeries, a range of baseline blood eosinophil counts, and those with and without comorbid asthma or comorbid AERD. Together, these data demonstrate a range of clinical benefits with mepolizumab regardless of prior SCS use and provide support for the SCS-sparing effects of mepolizumab in

TABLE I. Study outcomes by number of SCS courses received in the year before study entry

Outcome	0 SCS course in the year before the study		1 SCS course in the year before the study		>1 SCS course in the year before the study	
	Placebo (N = 201)	Mepolizumab (N = 206)	Placebo (N = 201)	Mepolizumab (N = 206)	Placebo (N = 201)	Mepolizumab (N = 206)
Change from baseline in total endoscopic NP score at week 52*						
n	110	100	47	64	44	42
≥5-point improvement, n (%)	1 (<1)	3 (3)	0	2 (3)	1 (2)	1 (2)
4-point improvement, n (%)	2 (2)	7 (7)	1 (2)	4 (6)	2 (5)	5 (12)
3-point improvement, n (%)	7 (6)	15 (15)	3 (6)	6 (9)	1 (2)	2 (5)
2-point improvement, n (%)	5 (5)	11 (11)	1 (2)	12 (19)	2 (5)	6 (14)
1-point improvement, n (%)	19 (17)	11 (11)	7 (15)	14 (22)	5 (11)	5 (12)
No change, n (%)	41 (37)	30 (30)	21 (45)	17 (27)	21 (48)	10 (24)
Worsening, n (%)	35 (32)	23 (23)	14 (30)	9 (14)	12 (27)	13 (31)
Median change from baseline	0.0	0.0	0.0	−1.0	0.0	0.0
Difference in medians (95% CI)	−0.52 (−1.01 to −0.04)		−1.00 (−1.51 to −0.49)		−0.43 (−1.25 to 0.39)	
Change from baseline in nasal obstruction VAS score at weeks 49-52*						
n	110	100	47	64	44	42
>5-point improvement	25 (23)	46 (46)	11 (23)	31 (48)	10 (23)	14 (33)
>3- to 5-point improvement	19 (17)	13 (13)	4 (9)	9 (14)	4 (9)	11 (26)
>1- to 3-point improvement	20 (18)	10 (10)	4 (9)	5 (8)	3 (7)	7 (17)
≤1-point improvement to ≤1-point worsening	44 (40)	29 (29)	25 (53)	18 (28)	26 (59)	10 (24)
>1-point worsening	2 (2)	2 (2)	3 (6)	1 (2)	1 (2)	0
Median change from baseline	−1.75	−4.55	−0.04	−4.83	−0.03	−3.80
Difference in medians (95% CI)	−2.55 (−4.17 to −0.92)		−3.72 (−5.49 to −1.95)		−3.55 (−5.18 to −1.92)	
Change from baseline in SNOT-22 total score at week 52* (MCID, ≥8.9-point improvement) ³⁸						
n	110	100	47	64	44	42
≥45-point improvement	17 (16)	29 (29)	4 (9)	21 (33)	5 (11)	6 (15)
≥36- to 44-point improvement	6 (6)	16 (16)	3 (7)	7 (11)	1 (2)	7 (17)
≥27- to 35-point improvement	15 (14)	10 (10)	10 (22)	13 (20)	5 (11)	5 (12)
≥18- to 26-point improvement	15 (14)	11 (11)	2 (4)	5 (8)	5 (11)	6 (15)
≥9- to 17-point improvement	10 (9)	7 (7)	5 (11)	2 (3)	3 (7)	5 (12)
≥1- to 8-point improvement	8 (7)	3 (3)	2 (4)	3 (5)	3 (7)	2 (5)
No change	16 (15)	16 (16)	7 (15)	7 (11)	11 (25)	7 (17)
Worsening	21 (19)	8 (8)	13 (28)	6 (9)	11 (25)	3 (7)
Median change from baseline	−16.50	−31.00	−10.00	−32.00	−1.50	−22.00
Difference in medians (95% CI)	−17.02 (−26.16 to −7.88)		−22.57 (−39.16 to −5.98)		−16.16 (−27.67 to −4.65)	
Time to first sinus surgery						
Sinus surgery up to week 52, n (%)	21 (19)	9 (9)	13 (28)	6 (9)	12 (27)	3 (7)
Hazard ratio, [†] mepolizumab/placebo (95% CI)	0.62 (0.27 to 1.39)		0.30 (0.10 to 0.86)		0.17 (0.04 to 0.68)	

CI, Confidence interval; MCID, minimal clinically important difference; NP, nasal polyps; SCS, systemic corticosteroid; SNOT-22, sino-nasal outcomes test-22; VAS, visual analog scale.

*Patients with sinus surgery before time period are assigned their worst observed score before sinus surgery; patients with no sinus surgery who withdrew from study before visit are assigned their worst observed score before study withdrawal; patients with missing visit data are assigned their worst observed score before the missing visit; Quantile regression with covariates of treatment group, geographic region, baseline score, and log₁₀ baseline blood eosinophil count.

†Estimated from a Cox proportional hazards model with covariates of treatment group, geographic region, baseline total endoscopic score (centrally read), baseline nasal obstruction VAS score, log₁₀ baseline blood eosinophil count, and number of previous surgeries (1, 2, >2 as ordinal).

patients with recurrent, refractory CRSwNP. These findings are consistent with the clinical benefits and SCS-sparing effects of mepolizumab previously demonstrated in patients with severe eosinophilic asthma.^{22,30}

This analysis assessed the impact of SCS use in the year before SYNAPSE on several study outcomes. Mepolizumab improved total endoscopic NP score, nasal obstruction VAS score, and SNOT-22 total score versus placebo across subgroups of patients with 0, 1, and more than 1 SCS courses in the year before the study. Between-group differences were consistently higher in patients with 1 SCS course during the

previous year than in those who did not receive SCS in the year before the study, possibly reflecting greater disease severity in the patients requiring SCSs and therefore greater room for clinical improvement. However, this upward trend did not continue in those with more than 1 SCS course in the previous year, which may be due to the low number of patients in this subgroup. The reduction in occurrence of sinus surgery with mepolizumab versus placebo increased with increasing number of SCS courses in the year before the study, again likely reflecting disease severity in the subgroups with greater SCS dependence.

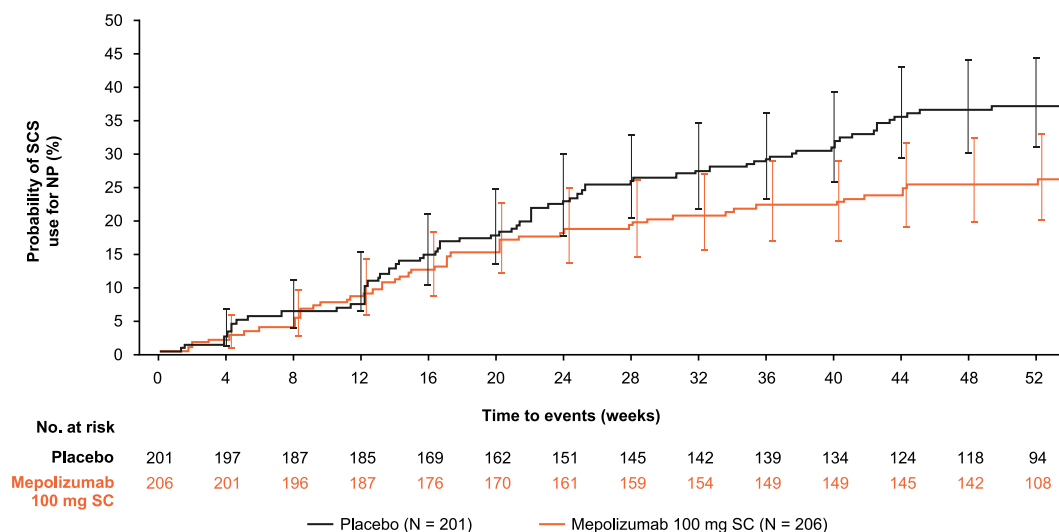


FIGURE 1. Time to first course of SCSs for NPs up to week 52 (ITT population). Vertical bars represent 95% CI. *CI*, Confidence interval; *ITT*, intent-to-treat; *NP*, nasal polyps; *SC*, subcutaneous; *SCS*, systemic corticosteroids.

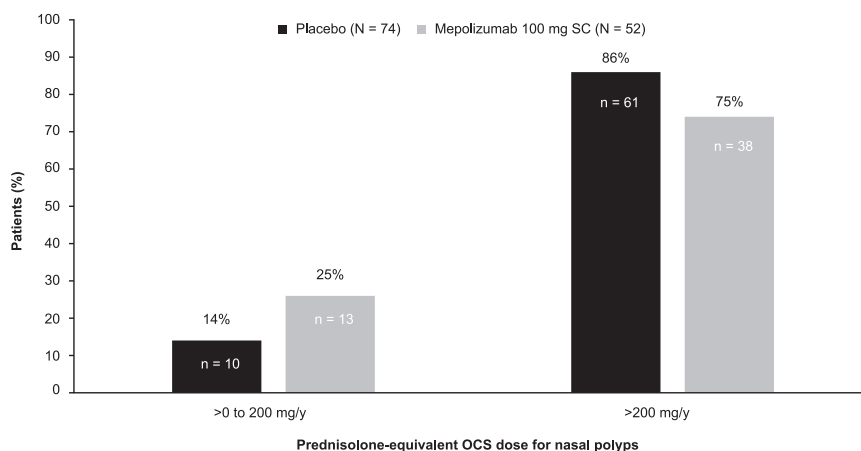


FIGURE 2. Prednisolone-equivalent OCS dose category for NPs during the 52-week treatment period in patients receiving 1 or more course of SCSs during the study. *Percentages calculated on the basis of 71 patients in the placebo group and 51 patients in the mepolizumab group with 1 or more course of SCSs during the study and with available OCS-dose data. *NP*, Nasal polyps; *OCS*, oral corticosteroid; *SC*, subcutaneous; *SCS*, systemic corticosteroid.

Approximately half the patients enrolled in SYNAPSE required at least 1 course of SCSs and more than 20% needed at least 2 courses of SCSs in the year before the study, highlighting that many were failing to achieve adequate disease control with standard of care therapy. During SYNAPSE, 75% of patients treated with mepolizumab received no courses of SCSs, compared with 63% of patients receiving placebo. For these patients, the reduced risk of SCS-associated adverse effects is an important benefit, given the high burden they bear.¹¹⁻¹⁵ Moreover, completing the 52-week study period with no SCS use is in line with treatment goals recommended in the most recent European Position Paper on Rhinosinusitis and Nasal Polyps, which include minimizing SCS courses to 2 or fewer per year in patients with partially controlled or uncontrolled NP.¹⁰

The baseline characteristics subgroup analysis presented here did not find any clinical characteristics that were predictive of the

need for SCS use during the study. Notably, the response to mepolizumab was variable, with most but not all patients in the mepolizumab group completing the study without the need for SCSs. Given the multiple inflammatory subtypes known to be present among patients with CRSwNP,⁴ it is tempting to speculate that patients who required SCSs during the study had a complex mix of inflammatory pathways contributing to their disease, including high levels of inflammation also driven by IgE, for example. All SYNAPSE patients had eosinophilic CRSwNP based on their baseline blood eosinophil counts; however, further research is needed to understand the relationship between blood and tissue levels of eosinophils and IL-5 in patients with CRSwNP. Investigation of other outcomes, such as olfaction, in the subset of patients who required SCSs despite mepolizumab treatment would be of interest, to determine whether improvements in other clinical outcomes were still observed. The present

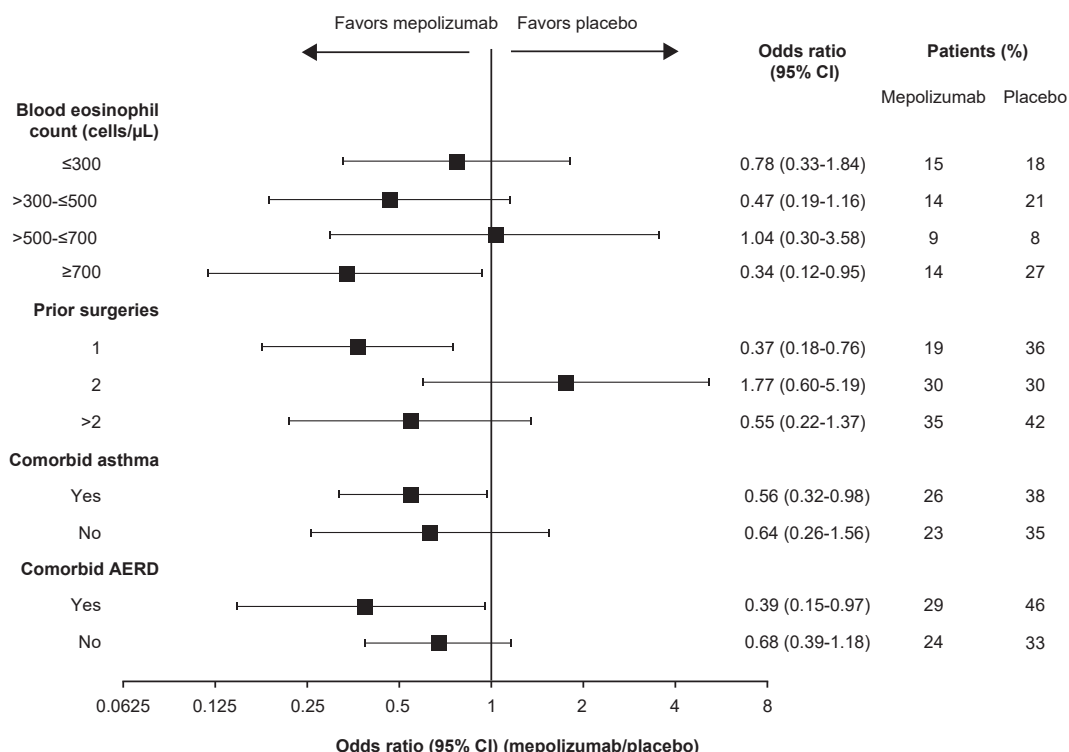


FIGURE 3. Proportion of patients requiring SCSs for NPs up to week 52 by baseline characteristic subgroups. Analysis using logistic regression model with covariates of treatment group, geographic region, number of SCS courses for NPs in last 12 months (0, 1, >1 as ordinal), baseline total endoscopic score (centrally read), baseline nasal obstruction VAS score, and \log_{10} baseline blood eosinophil count. Courses of systemic steroids separated by less than 7 days are considered a continuation of the same course. *AERD*, Aspirin-exacerbated respiratory disease; *CI*, confidence interval; *NP*, nasal polyps; *SCS*, systemic corticosteroid; *VAS*, visual analog scale.

TABLE II. Prednisolone-equivalent OCS dose by baseline characteristic subgroups

Baseline characteristic	Total prednisolone-equivalent OCS dose for NPs up to week 52 (mg/y), mean \pm SD	
	Placebo	Mepolizumab
Prior surgery		
1	151.7 \pm 334.8 n = 80	61.5 \pm 175.1 n = 108
2	149.0 \pm 349.9 n = 46	160.4 \pm 329.7 n = 47
>2	234.5 \pm 401.4 n = 72	164.2 \pm 310.3 n = 50
Baseline blood eosinophil count		
<150 cells/ μ L	147.4 \pm 380.4 n = 15	68.5 \pm 176.8 n = 20
≥ 150 cells/ μ L	183.9 \pm 363.7 n = 183	113.6 \pm 264.7 n = 185
<300 cells/ μ L	86.6 \pm 225.7 n = 61	94.7 \pm 238.8 n = 67
≥ 300 cells/ μ L	223.3 \pm 404.7 n = 137	116.2 \pm 266.6 n = 138
Comorbid asthma		
Yes	202.2 \pm 399.3 n = 146	119.3 \pm 277.8 n = 139
No	122.0 \pm 232.3 n = 52	87.8 \pm 208.6 n = 66
Comorbid AERD		
Yes	231.5 \pm 409.4 n = 61	90.1 \pm 206.0 n = 44
No	158.8 \pm 341.3 n = 137	114.4 \pm 270.1 n = 161

AERD, Aspirin-exacerbated respiratory disease; *NP*, nasal polyps; *OCS*, oral corticosteroid

findings highlight the need for understanding of how symptoms relate to the underlying inflammatory processes in CRSwNP and for endotyping of those patients who are eligible for biologic

treatment, to identify potential therapeutic targets and predict response to treatment.¹⁰ For example, measurement of IL-5 to categorize patients on the basis of high or low IL-5 levels would be beneficial for predicting treatment response to mepolizumab and could potentially be carried out in a clinical laboratory setting. Interestingly, an analysis of the effect of blood eosinophil count on the response to mepolizumab in SYNAPSE suggested that higher counts were predictive of improvements in nasal obstruction VAS score but not total endoscopic NP score.³² However, patient numbers in the subgroups were low; thus, further investigation of blood eosinophil count as a potential biomarker of response to mepolizumab is warranted.

In addition to reducing the proportion of patients requiring SCSs during SYNAPSE, mepolizumab reduced the mean dose of prednisolone-equivalent OCSs over the year compared with placebo in those receiving SCSs. The mean total prednisolone-equivalent dose of 438.9 mg/y in the mepolizumab group (compared with 505.2 mg/y in the placebo group) was of particular clinical relevance given the results of a previous study in 2018. Price et al¹⁷ demonstrated a lower risk of several SCS-related adverse effects in patients with a cumulative SCS exposure of more than 0 mg to less than 500 mg, compared with those with exposures of 500 mg to less than 1000 mg.¹⁷ Furthermore, among those receiving at least 1 course of SCSs in the current SYNAPSE analysis, the proportion of patients receiving more than 200 mg prednisolone-equivalent OCSs per year was lower with mepolizumab than with placebo (75% vs 86%). This is important because a dose of 200 mg possibly reflects the typical treatment

schedule of 40 mg OCSs for 5 days. Of note, analyses of total prednisolone-equivalent OCS dose per year and proportions of patients receiving different category levels of OCSs were restricted to patients receiving at least 1 SCS course during the study.

The SYNAPSE study has a number of strengths, including allowing patients to continue to receive SCS rescue medication in the study; this may be more representative of real-world clinical practice than other phase III CRSwNP studies, such as the dupilumab LIBERTY NP SINUS studies in which patients who received SCSs had their worst pre-SCS end-point values used for analysis.³⁹ Study limitations include the *post hoc* nature of the subgroup analyses presented here as well as the low number of patients in some of the subgroups. Despite these limitations, these data provide a comprehensive picture of the SCS-sparing capabilities of mepolizumab in a population of adults with severe CRSwNP and highlights the potential for mepolizumab as an SCS-sparing agent in CRSwNP.

CONCLUSIONS

This analysis of the SYNAPSE study found that mepolizumab was associated with clinical benefits regardless of prior SCS use in patients with severe CRSwNP in need of repeat surgery and that mepolizumab is associated with an SCS-sparing effect in this patient population. These data support the use of mepolizumab as a valuable add-on treatment to standard-of-care CRSwNP therapy with an SCS-sparing effect that can both improve efficacy outcomes and reduce the adverse effect burden associated with SCS use in patients with recurrent, refractory, severe CRSwNP.

Acknowledgment

Editorial support (in the form of writing assistance, including preparation of the draft manuscript under the direction and guidance of the authors, collating and incorporating authors' comments for each draft, assembling tables and figures, and grammatical editing and referencing) was provided by Ciara Keogh, PhD, at Fishawack Indicia Ltd, UK, part of Fishawack Health, and was funded by GSK.

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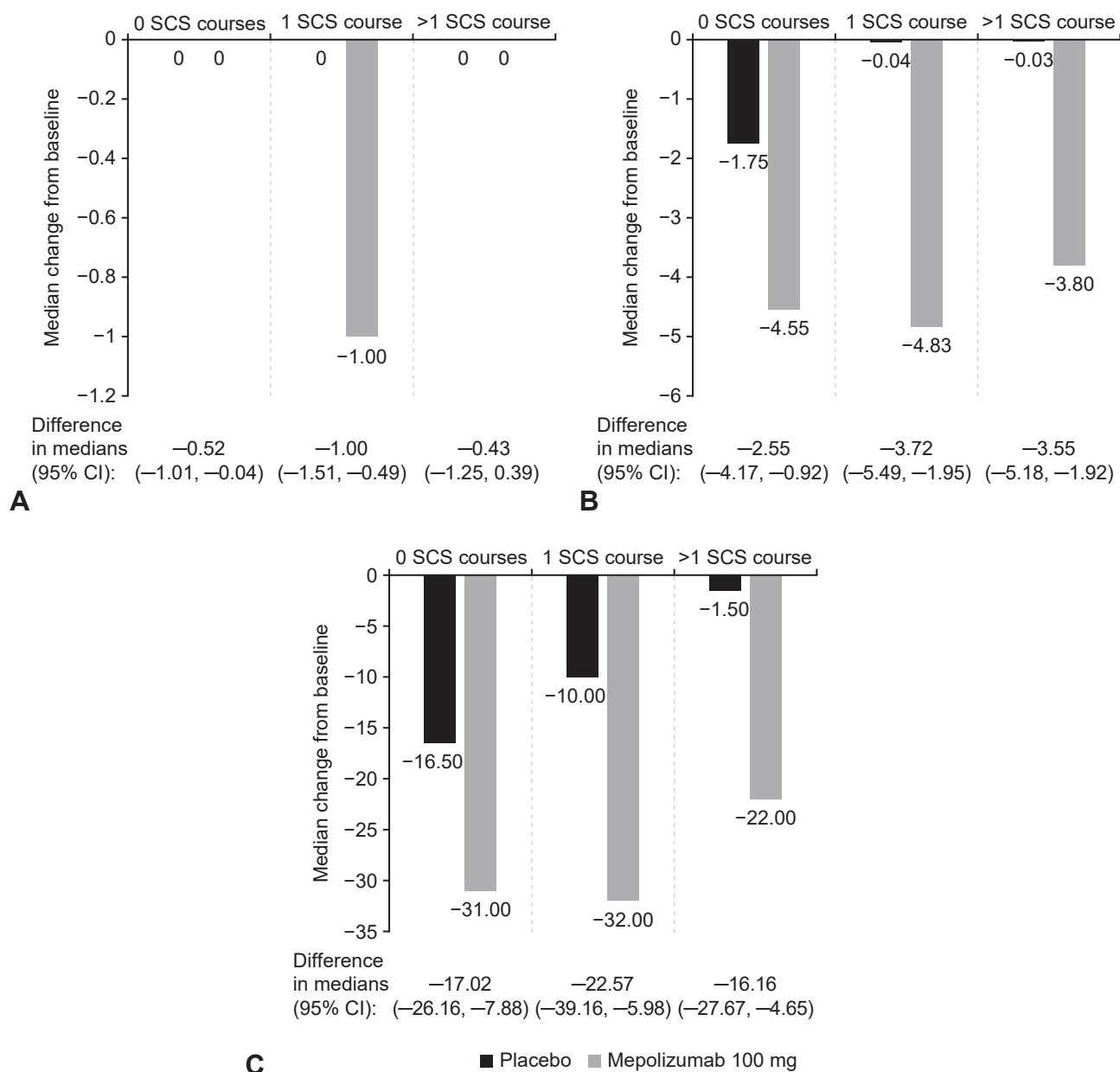


FIGURE E1. Study outcomes by number of SCS courses received in the year before study entry: **(A)** Change from baseline in total endoscopic NP score at week 52. **(B)** Change from baseline in nasal obstruction VAS score at weeks 49 to 52. **(C)** Change from baseline in SNOT-22 total score at week 52* (MCID, ≥ 8.9 -point improvement).^{E1} *Patients with sinus surgery before time period are assigned their worst observed score before sinus surgery; patients with no sinus surgery who withdrew from study before visit are assigned their worst observed score before study withdrawal; patients with missing visit data are assigned their worst observed score before the missing visit. MCID, Minimal clinically important difference; NP, nasal polyp; SCS, systemic corticosteroid; SNOT-22, Sino-Nasal Outcomes Test-22; VAS, visual analog scale.

TABLE E1. Prednisolone-equivalent OCS dose category for NPs during the 52-wk treatment period in patients receiving ≥ 1 course of SCSs for NPs during the study

Prednisolone-equivalent OCS dose for NP (mg/y)	Patients, n (%) [*]	
	Placebo (N = 74)	Mepolizumab (N = 52)
>0-100	5 (7)	9 (18)
>100-200	5 (7)	4 (8)
>200-300	18 (25)	9 (18)
>300-400	10 (14)	9 (18)
>400-500	12 (17)	2 (4)
>500-600	2 (3)	3 (6)
>600	19 (27)	15 (29)

NP, Nasal polyps; OCS, oral corticosteroid; SCS, systemic corticosteroid.
^{*}Percentages calculated on the basis of 71 patients in the placebo group and 51 patients in the mepolizumab group with ≥ 1 course of SCSs during the study and with available OCS-dose data.

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