

ORIGINAL ARTICLE

Sustained efficacy of mepolizumab in patients with severe chronic rhinosinusitis with nasal polyps: SYNAPSE 24-week treatment-free follow-up

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Additional supporting information, which includes a listing of members participating in the follow-up period, on which this analysis is based, can be found in the online version of this article.

Abstract

Background: In the 52-week Phase III SYNAPSE study, mepolizumab given every 4 weeks (100 mg subcutaneously) reduced nasal polyp (NP) size, improved symptoms and quality of life (QoL), and reduced corticosteroid use and number of sinus surgeries in patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP), versus placebo. Because the durability of mepolizumab's efficacy after discontinuation is poorly understood in CRSwNP, the efficacy of mepolizumab after discontinuation was analyzed in severe CRSwNP, over a 24-week follow-up.

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Methods: Changes from SYNAPSE baseline to end of treatment (week 52) and end of follow-up (week 76) were assessed for total endoscopic NP score, nasal obstruction and overall symptoms visual analog scale scores, and 22-item Sino-Nasal Outcome Test score. Time to first sinus surgery, time to first corticosteroid use, and geometric mean blood eosinophil counts (BECs) were also assessed.

Results: Among 134 follow-up patients, clinical improvements observed with mepolizumab versus placebo were partially evident 24 weeks after discontinuation despite BEC returning to baseline. The mean (95% confidence interval [CI]) change from baseline in NP score (week 52: -1.3 [1.8 to -0.9] vs. -0.3 [-0.6 to 0.1]; week 76: -1.2 [-1.6 to -0.7] vs. -0.1 [-0.5 to 0.3]) and the proportion of patients having sinus surgery (week 52: 4% vs. 25%; week 76: 9% vs. 31%) remained substantially improved with mepolizumab versus placebo. Mepolizumab-associated improvements in overall symptoms, quality of life, and corticosteroid use versus placebo were partially sustained at week 76.

Conclusion: Fifty-two weeks of mepolizumab treatment is associated with sustained clinical benefits up to 24 weeks after discontinuation in patients with severe CRSwNP, which should be considered by physicians when making treatment decisions.

KEYWORDS

biologic therapy, chronic rhinosinusitis with nasal polyps, durability, efficacy, mepolizumab, sinus surgery

1 | INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterized by chronic, predominantly eosinophilic type 2 inflammation of the nose and paranasal sinuses, causing the formation of NP.^{1–4} In addition to endoscopic evidence of NP, patients with severe disease experience 2 or more persistent symptoms (including nasal obstruction, nasal discharge and/or postnasal drip, facial pain or pressure, and loss of smell and/or taste), which can have a detrimental impact on their quality of life (QoL).^{5–7} Moreover, patients with CRSwNP typically have comorbid severe asthma and may have nonsteroidal anti-inflammatory drug-exacerbated respiratory disease.^{4,6}

Current standard-of-care (SoC) treatments for CRSwNP include intranasal corticosteroids, short-term antibiotics, and/or systemic corticosteroids (SCS) and sinus surgery.⁸ Although SCS can temporarily reduce NP size and improve associated symptoms, their long-term use is associated with adverse effects.^{6,9} Moreover, patients with severe disease who do not achieve adequate disease control with SoC pharmacologic treatments often require repeat sinus surgeries, which can accumulatively lead to scarring or mucosal damage.^{10–12} Biologic therapies targeting

type 2 inflammatory cytokines are now also recommended as add-on treatments for patients with severe CRSwNP.^{5,8,13} Among these, mepolizumab is a humanized monoclonal antibody that targets interleukin-5 (IL-5), the primary cytokine responsible for the proliferation, activation, and survival of eosinophils.¹⁴ In the 52-week Phase III SYNAPSE study, mepolizumab 100 mg (administered subcutaneously [SC] every 4 weeks, as an add-on to SoC) reduced NP size, improved disease symptoms, and reduced the need for SCS and sinus surgery in patients with severe CRSwNP, versus placebo.¹⁵ Importantly, patients' disease-specific QoL also significantly improved with mepolizumab versus placebo, with a between-treatment reduction almost twice the minimal clinically important difference (MCID; 8.9 points or higher¹⁶) for 22-item Sino-Nasal Outcome Test (SNOT-22) total score.¹⁵

The sustainability of clinical efficacy after discontinuation of biologics is poorly understood among patients with severe CRSwNP. In addition, outside of a clinical trial setting, it is uncommon for patients to have complete adherence to biologic therapies.¹⁷ Reasons for nonadherence are often complex, and, in patients with severe eosinophilic asthma receiving biologics, missed doses or temporary access issues can stem from work/family commitments,

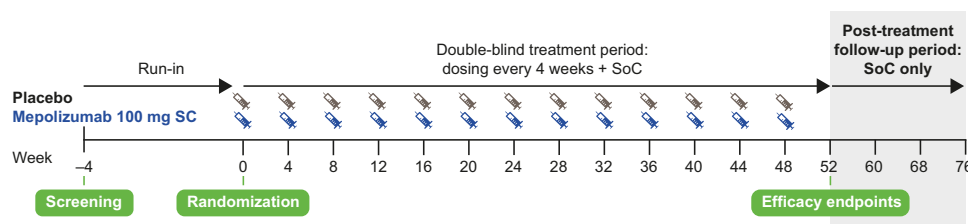


FIGURE 1 Study design. SoC included daily mometasone furoate nasal spray and (if required) saline nasal douching and short courses of oral corticosteroids (and/or antibiotics). SC, subcutaneous; SoC, standard of care.

insurance/financial/travel issues, and patients' own perception of disease control.¹⁷ The real-world clinical impact of incomplete adherence to biologics is yet to be assessed in patients with CRSwNP. Disease remission (i.e., an absence of symptoms or disease progression) is also an elusive goal for patients with CRSwNP and needs further investigation. Moreover, although it has been proposed that biologic treatment response should be assessed after 16 weeks of uninterrupted treatment in patients with CRSwNP,⁸ an optimal minimum duration before clinical assessment has not yet been established. In this analysis of SYNAPSE study data we aimed to determine whether the clinical benefits of mepolizumab could be maintained after cessation of 52 weeks of treatment, over a 24-week follow-up period.

2 | PATIENTS AND METHODS

2.1 | Study design and treatment

SYNAPSE (GSK ID: 205687/NCT03085797) was a Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of mepolizumab add-on treatment in adults with severe CRSwNP. Study details and eligibility criteria have been published previously.¹⁵ Briefly, 414 patients were randomized 1:1 to receive mepolizumab 100 mg SC or placebo every 4 weeks for 52 weeks, in addition to SoC treatment (daily mometasone furoate nasal spray and [if required] saline nasal douching and short courses of oral corticosteroids and/or antibiotics). After the treatment period, up to the first 200 randomized patients could be sequentially enrolled into a 24-week treatment-free follow-up period, up to week 76 (Figure 1).¹⁵ SYNAPSE was performed in accordance with ethical principles of the Declaration of Helsinki, Good Clinical Practice guidelines from the International Conference on Harmonization, 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 participating sites. The protocol is available at <https://www.gskstudyregister.com>.

2.2 | Patients

Eligible patients were ≥ 18 years of age and had severe bilateral NP (total endoscopic NP score ≥ 5 [≥ 2 in each nasal cavity], nasal obstruction visual analog scale [VAS] score > 5 , and overall symptom VAS score > 7), at least 1 sinus surgery in the last 10 years, and ≥ 8 weeks of stable mometasone furoate maintenance treatment before screening. All patients demonstrated at least 2 different sinonasal symptoms, including nasal blockage, obstruction, congestion, and/or discharge for ≥ 12 weeks before screening, plus facial pain or pressure and/or a reduction in or complete loss of smell (as per the latest European Position Paper on CRSwNP at the time).⁶ Patients who entered the 24-week follow-up period (the follow-up population) continued receiving SoC treatment throughout.

2.3 | End-points and assessments

To investigate the durability of mepolizumab's clinical efficacy after treatment cessation, changes from baseline in total endoscopic NP score and nasal obstruction VAS score (SYNAPSE coprimary end-points) were assessed in the follow-up population from week 52 to week 76 and from weeks 49 to 52 to weeks 73 to 76, respectively. The proportions of patients achieving at least a 1-point improvement from baseline in total endoscopic NP score and at least a 3-point improvement from baseline in nasal obstruction VAS score (both exploratory end-points, with nasal obstruction VAS analyzed post hoc) were also assessed in the follow-up population at these time-points. Overall symptoms VAS score and SNOT-22 total score (secondary end-points) were assessed in the follow-up population from weeks 49 to 52 to weeks 73 to 76 and from weeks 52 to 76, respectively. In addition, the proportion of patients achieving MCID (≥ 8.9 -point improvement) from baseline in SNOT-22 total score (exploratory end-point) was assessed. Time to first sinus surgery (secondary end-point) was assessed from baseline to week 76 in the follow-up population. Post hoc, time to first SCS use was assessed from baseline to week 76 in the overall follow-up

population and the previously described changes from baseline in NP score, VAS scores, and SNOT-22 total score were assessed in subgroups of follow-up patients without sinus surgery or without SCS use during the study period (patients with surgery or with SCS use during SYNAPSE were excluded from each of these subgroups, respectively). Pharmacokinetic and pharmacodynamic analyses included mepolizumab plasma concentrations (observed and predicted values at weeks 52 and 68) in all randomized patients who received at least 1 dose of mepolizumab, and absolute peripheral blood eosinophil counts (from baseline to week 76) in follow-up patients who received mepolizumab or placebo. Pharmacokinetic samples taken on dosing days were obtained before mepolizumab dosing. Safety end-points (adverse events [AEs], serious AEs, local injection-site reactions, and systemic reactions, coded according to the Medical Dictionary for Regulatory Activities version 22.1) were monitored during the treatment-free follow-up period in all randomized patients who received at least 1 dose of mepolizumab or placebo. For all analyses, baseline was defined as the SYNAPSE study baseline (i.e., before the first dose of study treatment was received).

2.4 | Statistical analysis

Descriptive statistics were used to report mean (95% confidence interval [CI]) changes from baseline in total endoscopic NP score, VAS scores, and SNOT-22 total score, in addition to the proportions of patients achieving the predefined improvements in these scores. Analyses of treatment differences (odds ratio, mepolizumab/placebo) in the proportions of patients achieving predefined improvements in total endoscopic NP score, nasal obstruction VAS score, and SNOT-22 total score were performed post hoc using a logistic regression model with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count. Time to first sinus surgery and first SCS use was analyzed via Kaplan–Meier estimates. Mepolizumab plasma concentrations were displayed using mean, median, interquartile range, and 95% CI; blood eosinophil counts were described by geometric mean and 95% CI. All data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA). The SYNAPSE study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03085797; GSK ID: 205687).

3 | RESULTS

3.1 | Patient population

Overall, 134 patients (mepolizumab $n = 69$, placebo $n = 65$) were included in the follow-up population. As previously

reported, the decision was made to stop consenting additional patients after the first 134 were recruited into the posttreatment follow-up period.¹⁵ This was to ensure that SYNAPSE study completion was determined by the last patient to complete the 52-week treatment duration, and not by completion of the final follow-up visit for the last patient recruited into the follow-up period.¹⁵ A total of 202 patients randomized to mepolizumab were included in the pharmacokinetic analysis, 49 and 67 of whom had observed and predicted data available at week 68, respectively. Baseline demographics and clinical characteristics for the SYNAPSE ITT patient population have been described previously¹⁵; the clinical characteristics of the follow-up population at baseline, week 52, and week 76 are presented in Table 1.

3.2 | Endoscopic NP score

At week 52 of SYNAPSE, improvements from baseline in total endoscopic NP score were larger with mepolizumab than placebo in the follow-up population, overall and in the no-surgery and no-SCS subgroups (Figure 2A–C). This treatment difference was robustly maintained throughout the treatment-free follow-up period (mean [95% CI] change from baseline to week 76 with previous mepolizumab vs. placebo: -1.2 [-1.6 to -0.7] vs. -0.1 [-0.5 to 0.3] overall to -1.4 [-1.8 to -1.0] vs. -0.5 [-1.0 to 0.0] without surgery and -1.6 [-2.1 to -1.1] vs. -0.4 [-1.0 to 0.2] without SCS; Figure 2A–C). The proportion of follow-up patients achieving at least a 1-point improvement from baseline in total endoscopic NP score was larger in the mepolizumab group than the placebo group at weeks 52 and 76 (week 52: 44 of 69 [64%] vs. 19 of 65 [29%] patients in the mepolizumab vs. placebo groups; odds ratio 4.56 [95% CI 2.15 to 9.67]; week 76: 41 of 69 [59%] vs. 18 of 65 [28%] patients in the mepolizumab vs. placebo groups; odds ratio 3.89 [95% CI 1.85 to 8.16]).

3.3 | Nasal obstruction VAS

Larger improvements in nasal obstruction were observed from baseline to weeks 49 to 52 with mepolizumab versus placebo in the follow-up population, overall and in the no-surgery and no-SCS subgroups (Figure 3A–C). After treatment cessation, mepolizumab-treated patients continued to experience less nasal obstruction than at baseline, and numerically larger improvements from baseline than those who had received placebo (mean [95% CI] change from baseline in nasal obstruction VAS score at weeks 73 to 76 with mepolizumab vs. placebo: -4.0 [-4.8 to -3.2]

TABLE 1 Demographics and clinical characteristics of patients in the follow-up population at baseline, week 52, and week 76.

	Baseline		Week 52		Week 76	
	Placebo (N = 65)	Mepolizumab 100 mg SC (N = 69)	Placebo (N = 65)	Mepolizumab 100 mg SC (N = 69)	Placebo (N = 65)	Mepolizumab 100 mg SC (N = 69)
Patients by region, n (%)	26 (40)	30 (43)	—	—	—	—
Europe	6 (9)					
USA	33 (51)	5 (7)				
Rest of world		34 (49)				
Total NP score*, mean (SD)	5.6 (1.4)	5.6 (1.1)	5.3 (2.0)	4.3 (1.8)	5.5 (1.88)	4.4 (1.90)
Nasal obstruction VAS score*, mean (SD)	8.9 (0.8)	9.0 (0.8)	6.2 (3.3)	3.7 (3.2)	6.3 (3.5)	5.0 (3.4)
Overall VAS score*, mean (SD)	9.0 (0.7)	9.1 (0.8)	6.3 (3.3)	3.8 (3.3)	6.4 (3.4)	4.8 (3.5)
SNOT-22 total score†, mean (SD)	63.1 (19.4)	67.9 (17.2)	46.0 (27.0)	26.8 (21.0)	46.4 (28.4)	39.3 (24.3)
Baseline blood eosinophil counts (cells/ μ L), geometric mean (SD logs)	410 (0.7)	390 (0.7)	380 (0.7)	70.0 (0.8)	440 (0.7)	440 (0.8)

Abbreviations: NP, nasal polyps; SC, subcutaneous; SD, standard deviation; SNOT-22, 22-item Sino-Nasal Outcome Test; VAS, visual analog scale.

*Higher scores indicate greater disease severity.

†Higher scores indicate worse quality of life.

vs. -2.6 [-3.4 to -1.7] overall to -4.4 [-5.2 to -3.6] vs. -3.9 [-4.8 to -2.9] without surgery to and -4.7 [-5.7 to -3.8] vs. -3.7 [-4.9 to -2.5] without SCS; Figure 3A–C). The proportion of follow-up patients achieving at least a 3-point improvement from baseline in nasal obstruction VAS score was greater in the mepolizumab group than in the placebo group at weeks 49 to 52 (53 of 69 [77%] vs. 28 of 65 [43%] patients; odds ratio 4.48 [95% CI 2.10 to 9.55]) and at weeks 73 to 76 (37 of 69 [54%] vs. 27 of 65 [42%] patients; odds ratio 1.65 [95% CI 0.81 to 3.36]), with a less pronounced beneficial outcome observed by the end of the follow-up period. Therefore, there was an overall reduction in beneficial outcome by the end of the follow-up period.

3.4 | Overall symptoms VAS

Mepolizumab-treated patients in the follow-up population had larger improvements from baseline in overall sinonasal symptoms by weeks 49 to 52 compared with those who received placebo, overall and in the no-surgery and no-SCS subgroups (Figure 4A–C). After treatment cessation, numerically larger improvements from baseline in overall symptoms VAS score were observed in mepolizumab-treated patients compared with those who had received placebo, overall (mean [95% CI] change from baseline to weeks 73 to 76: -4.3 [-5.11 to -3.4] vs. -2.6 [-3.4 to -1.8]; Figure 4A) and in the no-surgery (-4.7 [-5.5 to -3.9] vs. -3.9 [-4.8 to -2.9]; Figure 4B) and no-SCS

(-5.0 [-6.0 to -4.0] vs. -3.8 [-5.0 to -2.6]; Figure 4C) subgroups. In patients without surgery and without SCS use there was a reduction in beneficial outcome by the end of the follow-up period.

3.5 | SNOT-22 scores

Mepolizumab resulted in larger improvements from baseline to week 52 in disease-specific QoL versus placebo, in the overall follow-up population and in the no-surgery and no-SCS subgroups (Figure 5A–C). After treatment cessation, mepolizumab-treated patients continued to have better disease-specific QoL than those who had received placebo, as indicated by larger improvements from baseline in SNOT-22 score (mean [95% CI] change from baseline at week 76: -28.5 [-35.0 to -22.0] vs. -16.7 [-23.1 to -10.3] overall to -31.5 [-38.1 to -24.8] vs. -27.4 [-34.4 to -20.4] without surgery and -36.0 [-43.5 to -28.6] vs. -27.5 [-35.6 to -19.4] without SCS; Figure 5A–C). The proportion of follow-up patients achieving MCID in SNOT-22 total score was larger in the mepolizumab versus placebo group at week 52 (60 of 68 [88%] vs. 39 of 65 [60%] patients in the mepolizumab vs. placebo groups; odds ratio 4.83 [95% CI 1.96 to 11.86]) and week 76 (52 of 68 [76%] vs. 35 of 65 [54%] patients in the mepolizumab vs. placebo groups; odds ratio 2.27 [95% CI 1.27 to 5.80]), with a less pronounced beneficial outcome observed by the end of the follow-up period.

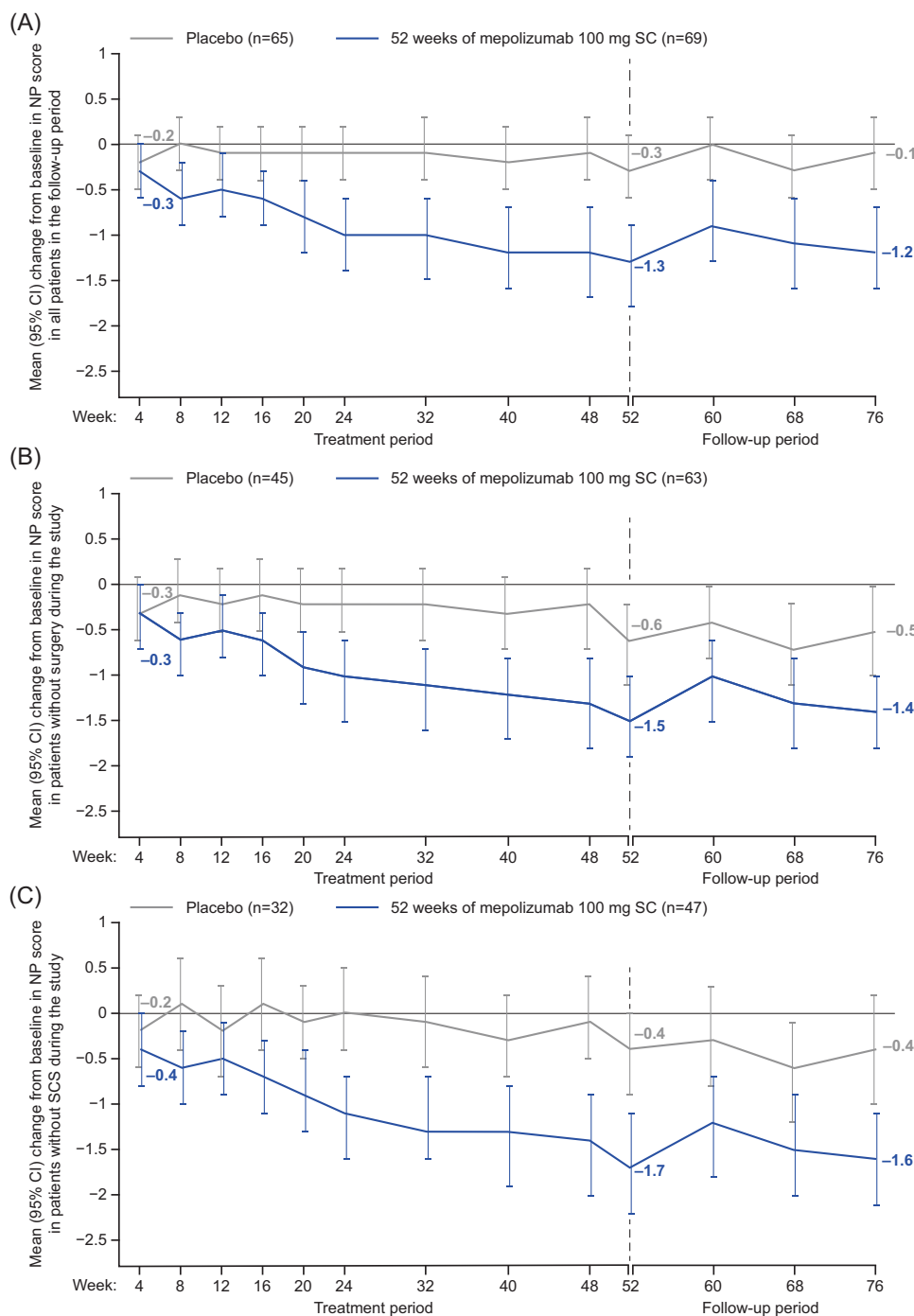


FIGURE 2 Change from baseline in NP score over time in the overall follow-up population (A) and follow-up patients without surgery (*) throughout the study (B), and follow-up patients without SCS (†) use throughout the study (C). Larger reductions in NP score indicate greater improvements in disease severity. Patients with sinus surgery, who withdrew from the study, or with missing data before the visit were assigned their worst observed score before sinus surgery or withdrawal. *Subset of patients with no sinus surgery at any time during the study (placebo, $n = 45$; mepolizumab, $n = 63$). †Subset of patients not receiving SCS for NP at any time during the study (placebo, $n = 32$; mepolizumab, $n = 47$). CI, confidence interval; NP, nasal polyp; SC, subcutaneous; SCS, systemic corticosteroids.

3.5.1 | Probability of surgery or SCS use

At week 52, mepolizumab-treated patients in the follow-up population had a lower probability of undergoing

sinus surgery than those receiving placebo (4% vs. 25%; Figure 6A). This was also the case at week 76 (9% vs. 31%). Mepolizumab-treated patients in the follow-up population also had a numerically lower probability of requiring SCS

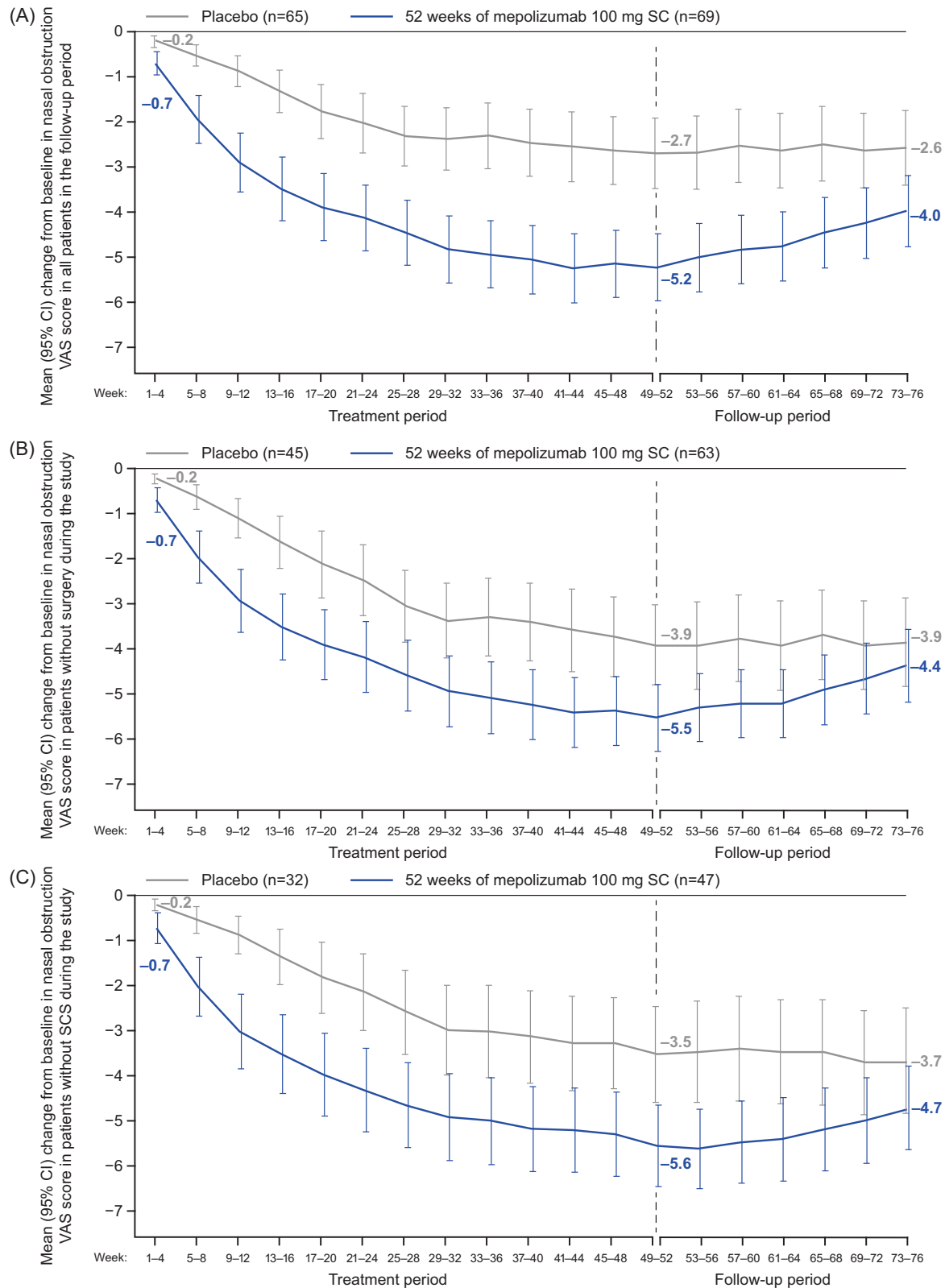


FIGURE 3 Change from baseline in nasal obstruction VAS score in the overall follow-up population (A) and follow-up patients without surgery (*) throughout the study (B), and follow-up patients without SCS (†) use throughout the study (C). Larger reductions in VAS score indicate greater improvements in disease severity. Patients with sinus surgery, who withdrew from the study, or with missing data before the visit were assigned their worst observed score before sinus surgery or withdrawal. *Subset of patients with no sinus surgery at any time during the study (placebo $n = 45$; mepolizumab $n = 63$). †Subset of patients not receiving SCS for NP at any time during the study (placebo, $n = 32$; mepolizumab, $n = 47$). CI, confidence interval; NP, nasal polyps; SC, subcutaneous; SCS, systemic corticosteroids; VAS, visual analog scale.

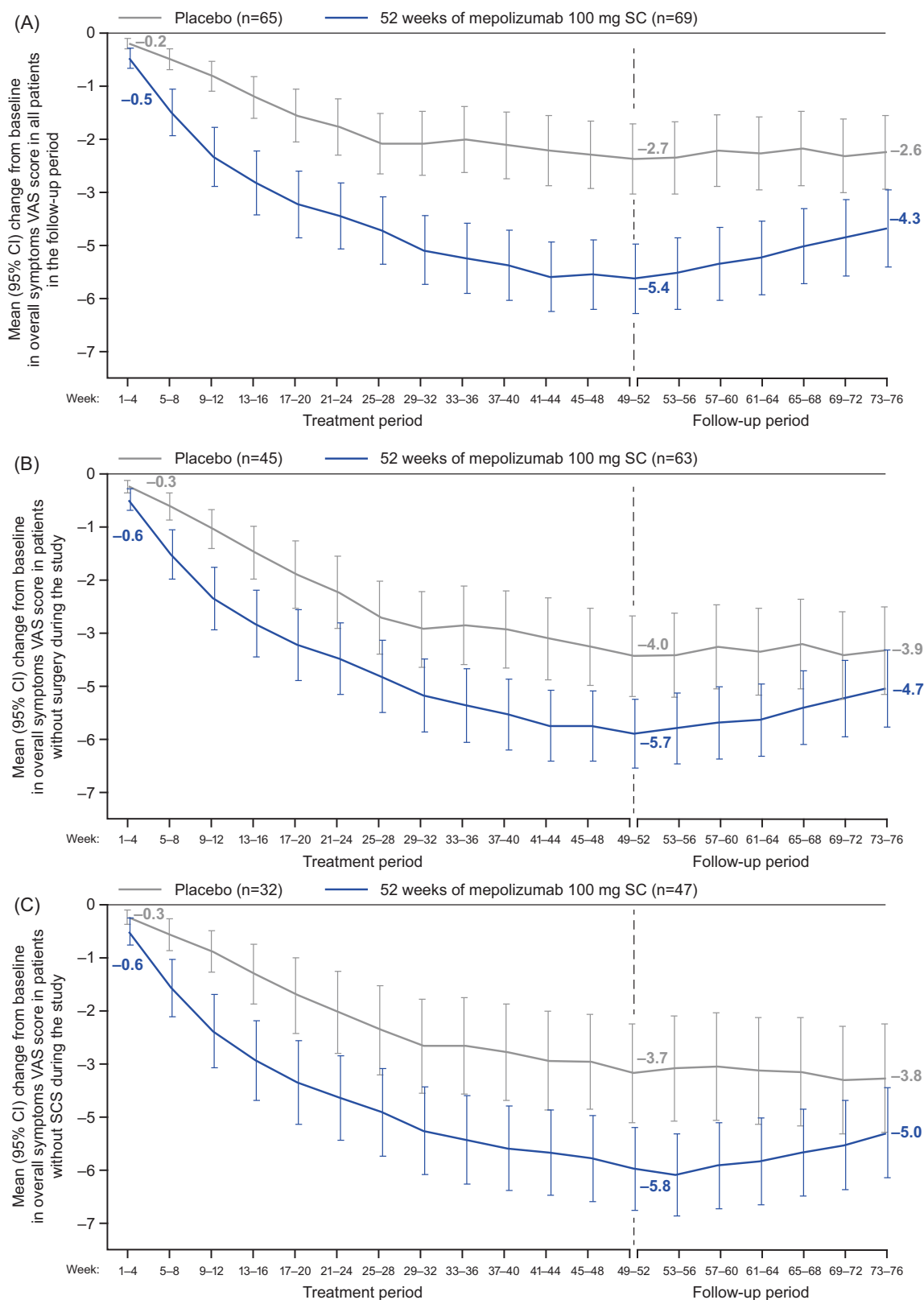


FIGURE 4 Change from baseline in overall symptoms VAS score in the overall follow-up population (A), follow-up patients without surgery (*) (B) throughout the study, and follow-up patients without SCS (†) use throughout the study (C). Larger reductions in VAS score indicate greater improvements in disease severity. Patients with sinus surgery, who withdrew from the study, or with missing data before the visit were assigned their worst observed score before sinus surgery or withdrawal. *Subset of patients with no sinus surgery at any time during the study (placebo, $n = 45$; mepolizumab, $n = 63$). †Subset of patients not receiving SCS for NP at any time during the study (placebo, $n = 32$; mepolizumab, $n = 47$). CI, confidence interval; NP, nasal polyps; SC, subcutaneous; SCS, systemic corticosteroids; VAS, visual analog scale.

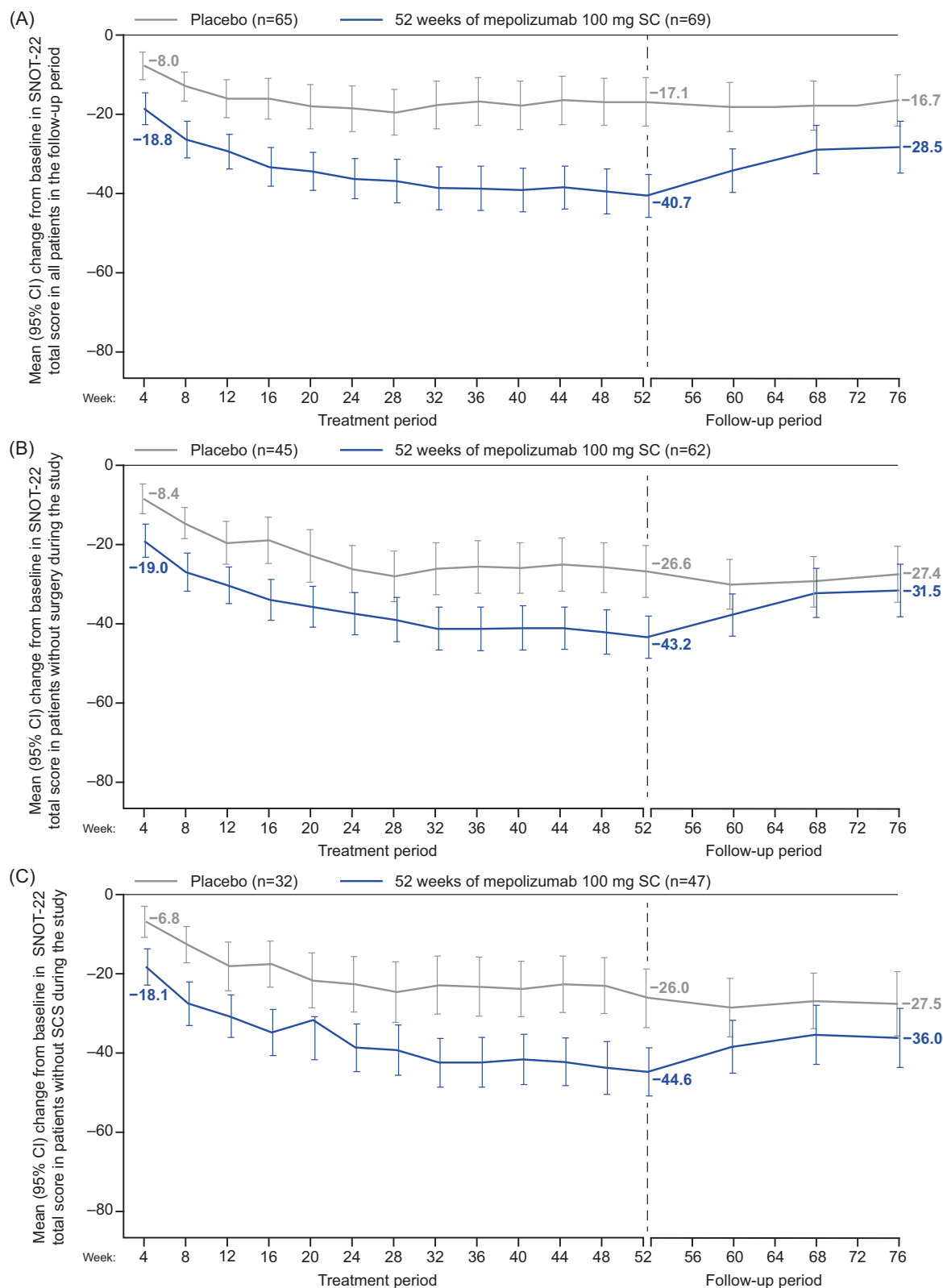


FIGURE 5 Change from baseline in SNOT-22 total score in the overall follow-up population (A) and follow-up patients without surgery (*) throughout the study (B), and follow-up patients without SCS (†) use throughout the study (C). Larger reductions in SNOT-22 total score indicate greater improvements in disease-specific quality of life. Patients with sinus surgery, who withdrew from the study, or with missing data before the visit were assigned their worst observed score before sinus surgery or withdrawal. *Subset of patients with no sinus surgery at any time during the study (placebo, $n = 45$; mepolizumab, $n = 63$). †Subset of patients not receiving SCS for NP at any time during the study (placebo, $n = 32$; mepolizumab, $n = 47$). CI, confidence interval; NP, nasal polyps; SC, subcutaneous; SCS, systemic corticosteroids; SNOT-22, 22-item Sino-Nasal Outcome Test.

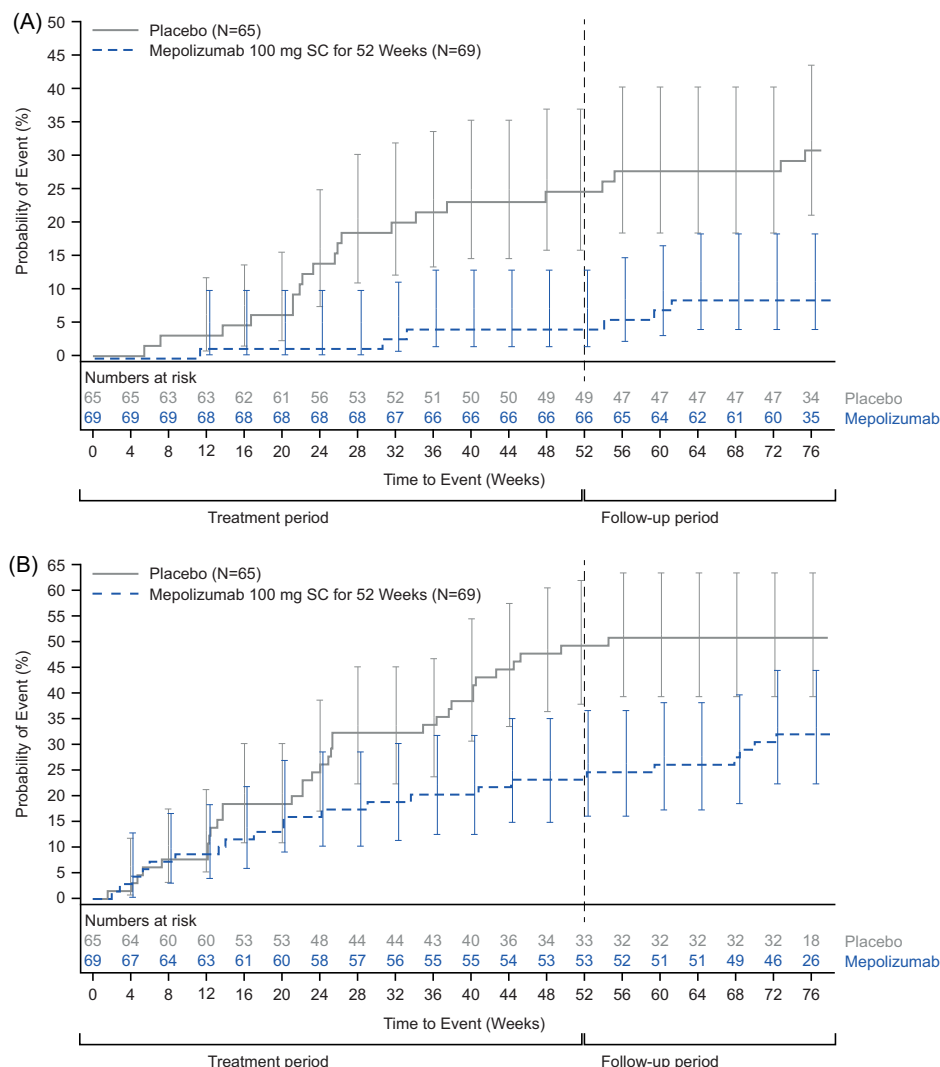


FIGURE 6 Kaplan–Meier estimate of time to first sinus surgery (A) and time to first course of SCS (B) for follow-up patients. Vertical bars represent 95% CIs. CI, confidence interval; SC, subcutaneous; SCS, systemic corticosteroids.

than those receiving placebo at week 52 (23% vs. 50%) and week 76 (30% vs. 50%), although, at week 76, the CIs of the mepolizumab and placebo probabilities were overlapping (Figure 6B).

3.5.2 | Pharmacokinetic and pharmacodynamic results

At week 52, mean (SD) observed and predicted mepolizumab plasma concentrations were 9679.6 (5367.13) ng/mL and 8732.7 (4181.91) ng/mL, respectively. By 16 weeks of treatment cessation (week 68), mean (SD) observed and predicted mepolizumab plasma concentrations were reduced to 877.2 (1884.24) ng/mL and 577.8 (1247.23) ng/mL. Mepolizumab versus placebo reduced blood eosinophil counts in the follow-up population by week 52 (Figure 7). After 16 weeks of treatment

cessation (week 68), blood eosinophil counts in the mepolizumab group had returned to pretreatment levels.

3.5.3 | Safety

Proportions of patients with AEs after week 52 were similar in the mepolizumab (46% [32 of 69]) and placebo (40% [26 of 65]) groups. Only headache (7%, 8%) and nasopharyngitis (9%, 6%) were reported for >5% of patients in the mepolizumab and placebo groups, respectively.

4 | DISCUSSION

The results of this analysis show that patients with severe CRSwNP receiving SoC treatment experience

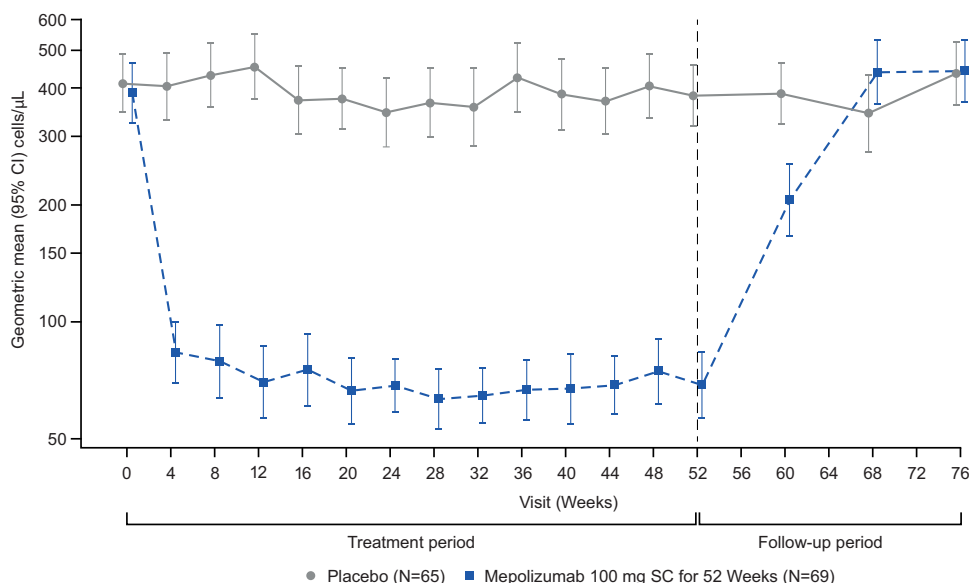


FIGURE 7 Blood eosinophil counts for follow-up patients. CI, confidence interval; SC, subcutaneous.

several clinical benefits with add-on mepolizumab versus placebo, which persist to some degree up to 24 weeks after treatment cessation. Interestingly, NP size and the risk of sinus surgery remained substantially reduced from baseline in the mepolizumab versus placebo group, despite peripheral blood eosinophil counts returning to pretreatment levels in mepolizumab-treated patients. Patient-reported symptoms and disease-specific QoL were improved with mepolizumab versus placebo at the end of the treatment period; although the magnitude of these improvements was reduced after treatment cessation, VAS and SNOT-22 scores remained below pretreatment levels and were lower in patients who had previously received mepolizumab versus placebo treatment. With regard to SNOT-22 total scores, improvements from baseline to the end of follow-up remained greater than the MCID (8.9 points)¹⁶ in the mepolizumab-treated group. The probability of SCS use increased marginally after week 52, but mepolizumab-treated patients remained less likely to need SCS during the follow-up period than placebo-treated patients. The pharmacokinetic and pharmacodynamic profiles of mepolizumab 100 mg were as expected; mepolizumab plasma concentrations decreased after mepolizumab discontinuation, which corresponded with blood-eosinophil counts returning to pretreatment levels. No new safety findings were identified for mepolizumab during the follow-up period.

In SYNAPSE, patients who underwent sinus surgery had their worst recorded presurgery VAS and SNOT-22 scores imputed for all postsurgery visits, to incorporate the event of surgery into the estimate of treatment effect.¹⁵ The post-hoc subgroup analysis reported here demonstrates that patients without sinus surgery (and

therefore without their worst observed scores carried forward) experienced mepolizumab-associated improvements in CRSwNP symptoms and disease-specific QoL similar to the overall follow-up population. Interestingly, patients who did not require SCS during SYNAPSE had the most durable clinical response to mepolizumab during follow-up, which may indicate less severe disease or a different disease phenotype in some patients. Another explanation for this may be that mepolizumab had a sustained downstream effect on IL-5 signaling despite blood eosinophil counts returning to baseline levels, but further research is needed to substantiate this hypothesis.

To our knowledge, this is the first publication formally focused on the duration of clinical impact after the cessation of long-term mepolizumab 100 mg SC in patients with severe CRSwNP. Another study in 30 patients with CRSwNP demonstrated sustained clinical improvements in sense of smell, NP size, and nasal airflow after two 750-mg doses of mepolizumab versus placebo, over a 44-week treatment-free follow-up.¹⁸ With regard to other biologics targeting type 2 inflammation, a meta-analysis of the Phase III dupilumab SINUS-24 and SINUS-52 trials found that patients treated with dupilumab for 24 weeks had worsened symptoms and higher NP scores after 24 weeks of stopping dupilumab (while still receiving SoC therapy).¹⁹ Conversely, those receiving continuous dupilumab for 52 weeks had improved symptoms up to week 52.¹⁹ This underscores the need for continuous dupilumab treatment for sustained symptom control in CRSwNP. In the Phase III OSTRO trial, benralizumab-treated patients experienced NP score increases after treatment cessation, whereas blood eosinophil counts approached baseline values.²⁰ Similarly, in a long-term efficacy study of omalizumab, NP

scores gradually worsened after treatment cessation, while staying below baseline levels.²¹

Several studies have assessed the durability of mepolizumab treatment in patients with severe eosinophilic asthma, concluding that, in this patient population, continuous, uninterrupted mepolizumab treatment is optimal and blood eosinophil count is a good indicator of treatment response.^{18,19,22–24} One of these studies also showed that, at 16 weeks after discontinuation of long-term mepolizumab treatment, blood eosinophils returned to baseline levels and asthma control worsened.²² However, the current analysis suggests that, in patients with CRSwNP, a similar return to pretreatment blood eosinophil levels (by 16 weeks) is not necessarily accompanied by a worsening in clinical outcomes within the same time-frame, indicating potential disease modification after anti-IL-5 therapy. Moreover, although a previous study concluded that high pretreatment baseline blood eosinophil counts are a good biomarker for identifying patients with CRSwNP who will respond to mepolizumab,²⁵ the results of this analysis suggests that blood eosinophils may not be as sensitive for monitoring actual treatment response in patients with severe CRSwNP. Future studies investigating the utility of blood versus local tissue eosinophils to monitor anti-IL-5 treatment responses in CRSwNP will therefore be important. Taken together, the present findings also indicate potential differences in the pathobiologic role of eosinophils and IL-5 in severe eosinophilic asthma and severe CRSwNP, and therefore the durability of clinical response to targeted IL-5 inhibition in these diseases. Indeed, recent evidence suggests that IL-5 can act on several cell types other than eosinophils (including plasma cells, B cells, mast cells, and airway epithelial cells), indicating that it may play an eosinophil-independent role contributing to CRSwNP pathobiology.²⁶ For example, evidence in humans has indicated the presence of functionally active IL-5 receptors on basophils, mast cells, neutrophils, plasma cells, and airway epithelial cells and fibroblasts.²⁷ However, additional research is required to substantiate this hypothesis.

The results of this analysis suggest that, although mepolizumab treatment should be continued in eligible patients with severe CRSwNP, targeted IL-5 inhibition with mepolizumab is associated with clinical benefits that can persist for up to 24 weeks after treatment cessation. These findings contribute to improving our limited knowledge on the durability of clinical benefits after biologic treatment. By scrutinizing an extended (24-week) period of mepolizumab cessation in a clinical trial population, our analysis has provided insight into the efficacy of mepolizumab under the influence of clinician and patient behaviors such as treatment holidays or incon-

sistent adherence, in the absence of extensive real-world data. Our analysis has also highlighted the need for further long-term and real-world studies to assess the true clinical effectiveness and durability of biologic therapies in severe CRSwNP, as the precise durability of symptomatic and clinical benefits described is unknown. Such studies may provide further insights into the potential of remission or disease modification, an area of clinical research in which knowledge gaps remain. Furthermore, future research on long-acting IL-5 inhibition will also need to address the relative durability of clinical benefits after treatment cessation.

There are several limitations to this study that should be considered when interpreting the results. The relatively small sample size means that the findings should be interpreted with caution. In addition, patients were aware that they were no longer receiving treatment during follow-up, which could result in worse patient-reported outcomes compared with the treatment period. The apparent disassociation between blood eosinophil count and sustained improvements in NP score and risk of sinus surgery may reflect the relatively short 24-week follow-up period. Alternatively, it could be speculated that blood eosinophil counts may not fully reflect IL-5 activity or tissue eosinophil counts in the upper respiratory tract, despite a demonstrated association between these measures in CRS.^{28,29} Future studies could examine longer follow-up periods after mepolizumab treatment to determine exactly how long clinical benefits persist. Also, although patients in this study stopped mepolizumab treatment after 52 weeks, it would be useful to examine longer term treatment with anti-IL-5 therapy. It should also be noted that, for several of the outcomes assessed, improvements from baseline to the end of follow-up were observed in the placebo arm; these improvements were smaller than those observed with mepolizumab treatment and may have been due to increased health-care visits and adherence to maintenance therapy as a result of taking part in the study. It is also plausible that this observed placebo effect would have waned in the continued absence of placebo treatment. Patients with a total endoscopic NP score ≥ 5 were included in SYNAPSE; a notable proportion of patients with severe uncontrolled CRSwNP do not have NP scores ≥ 5 and would therefore have been excluded from this analysis, thus limiting the number of available patients for the study and the potential external validity of the findings.⁵ Sequential enrollment into the follow-up cohort helped prevent enrollment bias, while selection bias was minimized due to the randomized nature of the trial. Any patients withdrawing from the 52-week treatment period due to complex disease may have affected how well the follow-up patient sample represented the SYNAPSE intent-to-treat population or, indeed,

the real-world CRSwNP population. However, given the high patient retention during SYNAPSE and that patients withdrew from the study for a variety of reasons,¹⁵ any selection bias was likely to be minimal.

In conclusion, keeping in mind with the ultimate treatment goal of achieving remission or disease modification, these findings suggest that targeted IL-5 inhibition with mepolizumab has a sustained positive impact in patients with severe CRSwNP over 24 weeks of posttreatment, which should be considered by clinicians when addressing real-world challenges with their patients. Such challenges may include determining an appropriate biologic therapy and assessing the potential real-world impact of incomplete adherence to treatment in patients with severe CRSwNP. The apparent dissociation between blood eosinophil counts and sustained improvements in NP score and risk of sinus surgery that was observed in this study also warrants further research.

AUTHOR CONTRIBUTIONS

Ana R. Sousa and Robert H Chan were involved in the conception or design of the study. Martin Desrosiers and Joseph K. Han contributed to the acquisition of data. All authors contributed to the analysis or interpretation of data, drafted the work, or revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

Martin Desrosiers has received clinical trial funding from AstraZeneca, GSK, Probionase Therapies, and Sanofi; has participated on advisory boards for Regeneron Pharmaceuticals, Inc., and Sanofi; and holds equity in Probionase Therapies. Zuzana Diamant has received honoraria or speaker fees serving on advisory boards or as a consultant from ALK, AstraZeneca, Antabio, Boehringer Ingelheim, Foresee Pharmaceuticals, GSK, QPS-Netherlands, and Sanofi-Genzyme-Regeneron, all outside the submitted work. Paolo Castelnovo has participated in advisory boards and received speaker fees from AstraZeneca, GSK, Novartis, Regeneron, and Sanofi Genzyme. Peter W.

Hellings is a speaker and/or recipient of research grants by Sanofi, Regeneron, Novartis, GSK, Stallergenes, ALK, and Viartis. Joseph K. Han has received consultancy fees from Sanofi Genzyme, Regeneron, Genentech, AstraZeneca, GSK, and Gossamer Bio. Anju T. Peters has received personal fees from Sanofi Regeneron; grants from Sanofi Regeneron, Optinose, and AstraZeneca; and has participated in advisory boards for Sanofi Regeneron, Optinose, AstraZeneca, and GSK. Philippe Gevaert has participated on advisory boards and received speaker fees from ALK-Abelló, Argenx, AstraZeneca, Genentech, GSK, Novartis, Regeneron, Roche, Sanofi Genzyme, and Stallergenes-Greer. Abigail Fuller is a contract resource for GSK. Jared Silver, Steven G. Smith, Ana R. Sousa, and Robert H. Chan are employees of GSK and hold stocks/shares.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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