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Evaluating treatment response to mepolizumab in patients with severe CRSwNP*

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Abstract

Background: The SYNAPSE study (NCT03085797) demonstrated that mepolizumab decreased nasal polyp (NP) size and nasal obstruction in patients with chronic rhinosinusitis with NP (CRSwNP).

Methods: SYNAPSE, a randomized, double-blind study, included patients with recurrent, refractory, severe CRSwNP, eligible for repeated surgery despite receiving standard of care (SoC). Patients received 4-weekly mepolizumab 100 mg or placebo subcutaneously plus SoC for 52 weeks. This post hoc analysis further characterized treatment responses and association with patient characteristics. The proportion of patients meeting any and each of five response criteria indicating improvement in disease-specific quality of life, NP size, nasal obstruction, loss of smell, and overall symptoms at Weeks 24 and 52, were assessed in subgroups: 1) no surgery; 2) neither surgery nor systemic corticosteroids (SCS).

Results: Of 407 patients in the intention-to-treat population, 381 and 343 patients had no sinus surgery by Weeks 24 and 52, respectively. More mepolizumab- versus placebo-treated patients without surgery by Weeks 24 and 52 met each response criteria. Of the mepolizumab-treated patients without surgery by Week 24, 109 (55%) responded across ≥ 3 criteria, increasing to 126 (67%) by Week 52. Similar response trends were seen for patients with neither surgery nor SCS by Weeks 24 and 52. At either timepoint, there were no major differences in baseline characteristics between mepolizumab-treated full- (5/5 categories) and non-responders (0/5 categories).

Conclusions: Most patients who completed SYNAPSE required neither surgery nor SCS use and in addition achieved a progressive and sustained clinical response to mepolizumab underscoring the therapeutic benefits of mepolizumab in severe CRSwNP.

Key words: biological products, disease-specific quality of life, mepolizumab, systemic corticosteroid use, nasal polyps

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is typically characterized by persistent eosinophilic inflammation of the paranasal sinuses with the presence of bilateral nasal polyps (NP) [1-3]. Symptoms of CRSwNP include nasal blockage, loss of smell, nasal discharge, and facial pain/pressure [4]. The burden of disease for patients with persistent and severe symptoms, unresponsive to the current standard of care is substantial [5, 6]. In addition to requiring frequent healthcare resource utilization and incurring significant direct and indirect medical costs, CRSwNP has a significant impact on patients' disease-specific quality of life (QoL) [5-9]. Current standard of care for severe CRSwNP includes intranasal corticosteroids and saline irrigations with short courses of systemic corticosteroids (SCS), generally reserved for exacerbations due to potential short- and long-term toxicity [10, 11]. Endoscopic sinus surgery is often performed when patients continue to be symptomatic despite appropriate medical therapy [12]. CRSwNP can recur often requiring further surgeries and repeated courses of SCS [13]. Consequently, new biologic therapies (including mepolizumab, dupilumab, and omalizumab) targeting different aspects of the type 2 (T2) inflammatory pathway (characterized by increased Immunoglobulin E [IgE], interleukin [IL]-4, IL-5, and IL-13 activity) have been developed, but the patient profile for optimal response to a given treatment option is unclear [14-18].

The humanized monoclonal antibody mepolizumab targets interleukin-5, the primary cytokine by which eosinophils respond to differentiation, activation, and survival [19-22]. Mepolizumab is approved for the treatment of severe eosinophilic asthma, eosinophilic granulomatosis with polyangiitis (EGPA), hypereosinophilic syndrome (HES), and CRSwNP in multiple regions worldwide [23, 24]. Data from the Phase III SYNAPSE study demonstrated that mepolizumab treatment, compared with placebo, decreased NP size and reduced nasal obstruction in patients with severe CRSwNP, in addition to reducing risk of surgery, use of SCS, and overall symptoms [15]. To date, the extent of patient responses to mepolizumab based on clinically meaningful thresholds have not been fully characterized. It is important to assess outcomes across several clinically relevant aspects of disease.

In this post hoc analysis of data from the SYNAPSE study, response to mepolizumab, in the context of requirements for further sinus surgery and SCS use, was assessed based on five response criteria. Criteria for clinical improvements in disease-specific QoL (assessed by Sino-nasal Outcome Test [SNOT]-22), NP size (assessed by endoscopic NP score), and patient reported nasal obstruction, loss of smell and overall symptoms (each assessed by Visual Analog Scale [12]) were defined. Additionally, the characteristics of responders and non responders were determined, as has been previously investigated in patients with severe asthma [25, 26]. The objective of this post hoc analysis of the SYNAPSE study was to determine the proportion of patients experiencing clinical improvements with mepolizumab based on these response criteria, and to describe the clinical characteristics of patients by their level of treatment response. The overall aim was to better characterize the patient population likely to derive the most benefit from mepolizumab treatment.

Materials and methods

Study design

The SYNAPSE study has been described in detail previously [15]. Briefly, SYNAPSE was a Phase III randomized, double-blind, placebo-controlled, parallel-group, multi-center trial (GSK205687; NCT03085797). Patients were randomized (1:1) to receive mepolizumab 100 mg subcutaneously or placebo every 4 weeks, for 52 weeks, in addition to standard of care, which included daily mometasone furoate intranasal spray, saline nasal irrigations, and courses of SCS and/or antibiotics as required. Patients could proceed to sinus surgery if deemed necessary based on the treating physician's assessment of clinical need.

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 any applicable country-specific regulatory requirements. All patients provided written informed consent. The study was approved by local ethics review boards of the participating sites.

Patients

Eligible patients were ≥18 years of age with recurrent severe bilateral NP symptoms (nasal obstruction symptom VAS score of >5 [maximum 10]) refractory to standard of care treatment. All patients demonstrated a current need for surgery, defined by an overall symptoms VAS score >7 (maximum 10) and an endoscopic bilateral NP score of ≥5 (maximum 8), with a score ≥2 in each nasal cavity. Patients were also required to have ≥1 sinus surgery in the prior 10 years, stable maintenance therapy for ≥8 weeks before screening, and study defined symptoms of CRS (nasal blockage/obstruction/congestion or anterior/posterior nasal drip, with ≥1 of the following additional symptoms: nasal discharge, reduction/loss of smell, or facial pain/pressure) for ≥12 weeks before screening. Patients with and without comorbid asthma were eligible for inclusion, although patients with an asthma exacerbation (worsening of asthma requiring SCS for ≥3 days or a single intramuscular corticosteroid dose, and/or an emergency department visit or hospitalization) during the 4 weeks before randomization were excluded. There was no minimum blood or tissue eosinophil count requirement.

Endpoints

During SYNAPSE, patients completed the SNOT-22 questionnaire every 4 weeks, with a recall period of 2 weeks. Each of the twenty-two questions were scored using a 0–5 scale (total score range 0–110; higher scores indicate worse disease-specific QoL).

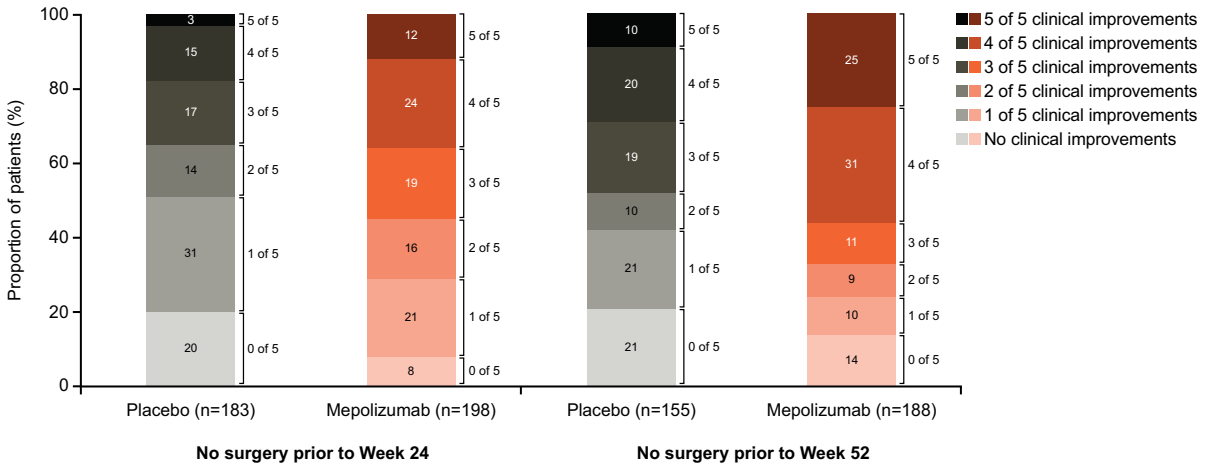

Figure 1. No surgery subgroup: Proportion of responders by number of clinical improvements* at Weeks 24 and 52. *Defined as improvement in: a) SNOT-22 total score (≥8.9-point); b) total endoscopic nasal polyp score (≥1-point); c) nasal obstruction VAS score (≥3-point); d) loss of smell VAS score (≥3-point); e) overall symptoms VAS score (≥2.5-point). SNOT-22, sinonasal outcome test-22; VAS, visual analog scale.

Total endoscopic NP score was assessed (blinded and centrally read), with each nostril scored using a 0–4 scale (total score: 0–8; higher score indicates larger polyps). Patients completed the 6 individual VAS (nasal obstruction, nasal discharge, throat mucus, loss of smell, facial pain, and overall symptoms) daily using a recall period of 24 hours. Patients quantified their symptom severity on an electronic device which represented the 0–10 cm paper scale, with 0 points conferring total absence of symptom(s) and 10 points conferring the worst thinkable severity of symptom(s). In this post hoc analysis, patients were classified as responders based on the following five criteria: 1) improved disease-specific QoL, determined by a ≥8.9-point improvement in SNOT-22 total score [27]; 2) reduced NP size, determined by a ≥1-point improvement in total endoscopic NP score; 3) reduced nasal obstruction, determined by a ≥3-point improvement in nasal obstruction VAS score; 4) improved loss of smell, determined by a ≥3-point improvement in loss of smell VAS score; and 5) improved overall symptoms, determined by a ≥2.5-point improvement in overall symptoms VAS score. The five response criteria were guided by the five criteria for assessing response to biological treatment outlined by the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) 2021, and the thresholds for meaningful within patient change in VAS scores identified in previous psychometric analyses of SYNAPSE data [4, 28]. All patients had minimum baseline SNOT-22, endoscopic NP, and VAS scores that permitted each patient to achieve a clinically meaningful response in each of the five criteria with the exception of loss of smell VAS (one patient had baseline score =0.94, where 0 is the best possible score, not permitting ≥3-point improvement) [15]. Achieving a response in each criteria was considered a clinical improvement.

Endpoints included the total number of clinical improvements achieved and the proportion of patients meeting each individual response criterion. Clinical improvement in ≥1 criteria was considered clinically meaningful. Responses were assessed at Week 24 and at Week 52 (see Statistical analysis).

Statistical analysis

Patient demographics and baseline characteristics were summarized descriptively by surgery status (with or without sinus surgery for removal of NP during the study) at Week 52; and by treatment response (patients who met none or all five response criteria) in patients without surgery by Week 24 and Week 52. Responder analyses were performed 1) at Week 24 in patients without surgery by Week 24; 2) at Week 52 in patients without surgery by Week 52; 3) at Week 24 in patients with neither surgery nor SCS use by Week 24; and 4) at Week 52 in patients with neither surgery nor SCS use by Week 52. These analyses were performed to determine the time course for mepolizumab treatment benefits, excluding any contribution of surgery to the reported outcomes, and to evaluate the impact of SCS use on this time course. Additionally, responder analyses for patients with surgery prior to Week 52 were performed using data from their last clinical visit prior to surgery to understand the response to mepolizumab treatment in these patients prior to the requirement for surgery. Data were included in the analysis regardless of treatment discontinuation. Patients with missing data due to study withdrawal or for any other reason, were considered non-responders.

Results

Patient population

Of the 407 patients included in the intent-to-treat population of the SYNAPSE study, 381 (94%) and 343 (84%) patients had not had further sinus surgery by Weeks 24 and 52, respectively (Figure S1). In total, 8 (4%) and 18 (9%) patients in the mepoli-

Table 1. Patient demographics and baseline characteristics by responder status in patients without surgery prior to Week 24 and 52.

	No surgery prior to Week 24 (n=381)				No surgery prior to Week 52 (n=343)			
	Placebo		Mepolizumab		Placebo		Mepolizumab	
	Met no response criteria at Week 24 (n=37)	Met all response criteria at Week 24 (n=5)	Met no response criteria at Week 24 (n=16)	Met all response criteria at Week 24 (n=24)	Met no response criteria at Week 52 (n=32)	Met all response criteria at Week 52 (n=16)	Met no response criteria at Week 52 (n=26)	Met all response criteria at Week 52 (n=47)
Age, years, mean (SD)	47.3 (15.53)	48.0 (5.34)	44.8 (15.39)	50.1 (13.61)	46.2 (11.65)	47.7 (10.42)	44.9 (14.16)	50.3 (12.64)
Female, n (%)	20 (54)	2 (40)	6 (38)	8 (33)	14 (44)	5 (31)	8 (31)	18 (38)
Duration of CRSwNP, years, mean (SD)	13.5 (9.76)	7.3 (2.55)	12.0 (7.50)	11.3 (7.66)	13.8 (6.61)	11.1 (6.70)	10.8 (6.67)	10.4 (7.02)
Blood eosinophil count, cells/µL, geometric mean (SD logs)	440 (0.674)	220 (1.203)	410 (0.764)	360 (0.774)	400 (0.647)	370 (0.874)	420 (0.685)	340 (0.760)
Comorbid conditions, n (%)								
Asthma	30 (81)	3 (60)	10 (63)	14 (58)	25 (78)	12 (75)	16 (62)	33 (70)
AERD/N-ERD	14 (38)	0	2 (13)	5 (21)	12 (38)	3 (19)	5 (19)	8 (17)
Allergic rhinitis	20 (54)	4 (80)	8 (50)	7 (29)	22 (69)	8 (50)	15 (58)	22 (47)
SNOT-22 total score (0-110), mean (SD)	n=34 62.2 (20.49)	n=5 9.2 (16.16)	n=16 62.2 (20.27)	n=24 55.9 (15.96)	n=30 63.4 (18.46)	n=16 58.2 (19.49)	n=26 65.0 (17.47)	n=47 59.9 (17.31)
Total endoscopic NP score (0-8, centrally read), mean (SD)	5.8 (1.32)	5.8 (1.48)	4.9 (0.93)	5.6 (1.06)	5.4 (1.01)	5.4 (1.46)	5.0 (1.15)	5.6 (0.99)
VAS score (0-10), mean (SD)								
Nasal obstruction	9.2 (0.80)	9.1 (0.67)	8.8 (0.90)	9.2 (0.76)	8.9 (1.08)	9.2 (0.60)	8.9 (0.83)	9.0 (0.82)
Loss of smell	9.7 (0.57)	9.5 (0.66)	9.6 (0.67)	9.8 (0.31)	9.7 (0.40)	9.6 (0.45)	9.6 (0.68)	9.7 (0.55)
Overall symptom	9.3 (0.69)	8.9 (0.54)	9.0 (0.86)	9.3 (0.73)	9.1 (0.84)	9.2 (0.49)	9.0 (0.84)	9.1 (0.69)
Composite – nasal symptoms	9.1 (0.89)	9.2 (0.58)	8.8 (0.91)	9.1 (0.67)	8.9 (0.94)	9.2 (0.47)	8.9 (0.81)	9.1 (0.65)
Time since most recent CRSwNP surgery, years, mean (SD)	n=37 3.7 (2.63)	n=5 2.7 (2.67)	n=16 5.1 (3.01)	n=24 3.6 (2.15)	n=31 4.3 (2.68)	n=16 3.6 (2.64)	n=26 4.2 (2.99)	n=47 4.1 (2.40)
Patients with ≥1 course of SCS for CRSwNP in the previous 12 months, n (%)	15 (41)	2 (40)	8 (50)	13 (54)	18 (56)	8 (50)	10 (38)	23 (49)

AERD, aspirin-exacerbated respiratory disease; N-ERD, nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease; NP, nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; SCS, systemic corticosteroids; SD, standard deviation; SNOT-22, sinonasal outcome test-22; VAS, visual analog scale.

zumab and placebo groups respectively had further surgery by Week 24, increasing to 18 (9%) and 46 (23%) patients by Week 52. Overall, patients with and without surgery by Week 52 had similar demographics and baseline characteristics (Table S1).

Response to mepolizumab in patients without surgery during SYNAPSE (no surgery subgroup)

Baseline characteristics

For patients without surgery during SYNAPSE, baseline charac-

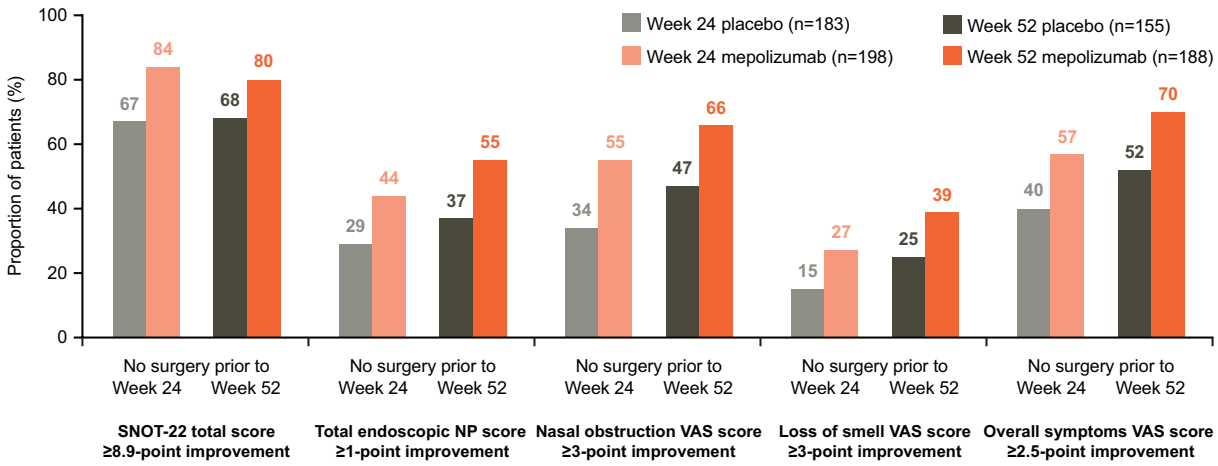

Figure 2. No surgery subgroup: Proportion of responders by individual responder criteria at Weeks 24 and 52. NP, nasal polyps; SNOT-22, sinonasal outcome test-22; VAS, visual analog scale.

teristics were compared between patients who met no response criteria (non-responders) and patients who met 5/5 response criteria (full-responders), in the mepolizumab and placebo arms, at Week 24 and Week 52 (Table 1). Among patients treated with mepolizumab there were no major differences in the majority of baseline characteristics between non-responders (n=16 at Week 24; n=26 at Week 52) and full-responders (n=24 at Week 24; n=47 at Week 52) at either Weeks 24 or 52. However, overall baseline blood eosinophil counts were numerically lower among full-responders versus non-responders (Table 1), although the number of patients in some subgroups in the placebo arm were small (n=5 full-responders at Week 24).

Response to treatment

Most patients without surgery during SYNAPSE achieved ≥1 clinical improvement with mepolizumab or placebo. This benefit was numerically greater with mepolizumab versus placebo at both Week 24 (182 [92%] vs 146 [80%] patients) and Week 52 (162 [86%] vs 123 [79%] patients) (Figure 1, Table S2). The proportion of patients meeting ≥3 clinical improvement criteria was also greater with mepolizumab versus placebo at both Week 24 (55% vs 35%) and Week 52 (67% vs 49%). This differentiation became more pronounced as the number of clinical improvements increased with 25% of patients treated with mepolizumab experiencing 5/5 clinical improvements at Week 52 compared to 10% of patients treated with placebo (Figure 1; Table S2). Moreover, there was a trend for patients to demonstrate a greater number of clinical improvements with time. For example, the proportion of patients treated with mepolizumab meeting ≥4 criteria increased from 36% at Week 24 to 56% at Week 52. Although the same trend for improvement between Weeks 24 and 52 was seen for placebo-treated patients, the overall number of responders was lower than in the mepolizumab-treated group (Figure 1, Table S2).

For each individual response criterion, the proportion of patients without surgery during SYNAPSE classified as responders at Week 24 or Week 52 was higher with mepolizumab than placebo (Figure 2). For patients who received mepolizumab, at both Week 24 and Week 52 the most common improvements were in SNOT-22 score, followed by overall symptoms VAS score, and nasal obstruction VAS score (Figure 2). The proportion of responders to each criterion increased between Weeks 24 and 52 in mepolizumab-treated patients, except for SNOT-22, where the proportion was similar (84% and 80%) (Figure 2).

Response to mepolizumab in patients with neither surgery nor SCS use during SYNAPSE (neither surgery nor SCS subgroup)

In total, of the 381 and 343 patients without surgery prior to Weeks 24 and 52, respectively, 315 (83%) and 266 (78%) patients also had no SCS use prior to these timepoints. The results for responders in each benefit criterion and the number of clinical improvements for patients with neither surgery nor SCS use were broadly consistent with those for patients without surgery, with the same trends for improvement between Week 24 and Week 52 (Figures 3 and 4; Table S2).

Response to mepolizumab in patients having surgery during SYNAPSE (surgery subgroup)

The proportion of patients achieving three, four, or five clinical improvements with mepolizumab was lower in patients who had surgery prior to Week 52 than those without surgery (Table S2, Table S3, Figure 5).

Of the 18 and 46 patients treated with mepolizumab and placebo, respectively, who had surgery prior to Week 52, a greater proportion of patients achieved a clinical response prior to surgery in SNOT-22 with mepolizumab, while the response for the two treatment groups was similar for the other response criteria (Figure S2). For patients treated with mepolizumab, the

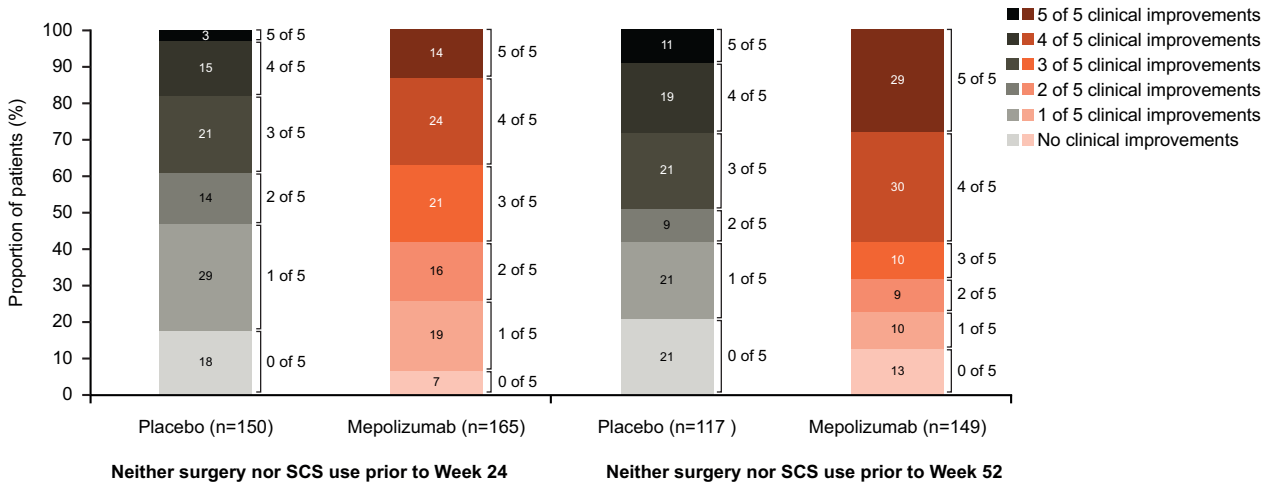

Figure 3. Neither surgery nor SCS subgroup: Proportion of responders by number of clinical improvements* at Weeks 24 and 52. *Defined as improvement in: a) SNOT-22 total score (≥8.9-point); b) total endoscopic nasal polyp score (≥1-point); c) nasal obstruction VAS score (≥3-point); d) loss of smell VAS score (≥3-point); e) overall symptoms VAS score (≥2.5-point). SCS, systemic corticosteroid; SNOT-22, sinonasal outcome test-22; VAS, visual analog scale.

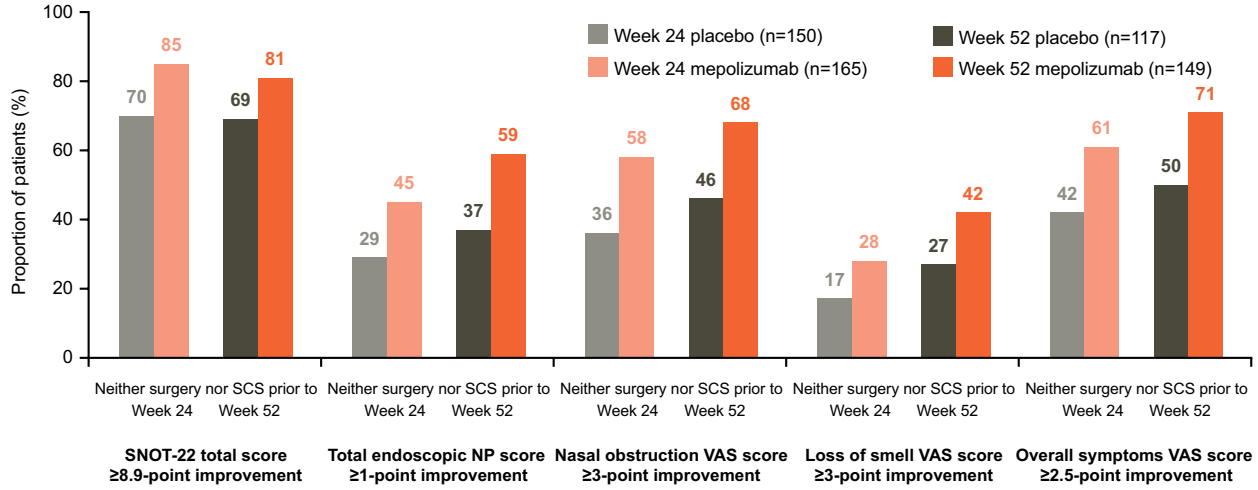

Figure 4. Neither surgery nor SCS subgroup: Proportion of responders by individual responder criteria at Weeks 24 and 52. NP, nasal polyps; SCS, systemic corticosteroid; SNOT-22, sinonasal outcome test-22; VAS, visual analog scale.

proportion of responders for any individual response criterion was lower in patients with surgery than without surgery by Week 52, except for the SNOT-22 score which was similar (83% response among patients with surgery vs 80% without surgery by Week 52) (Figure S2; Figure 2). The largest difference in response between patients receiving mepolizumab with and without surgery at Week 52 was in the nasal obstruction VAS score (22% vs 66%), although differences in overall symptoms VAS score (28% vs 70%), and loss of smell VAS score (6% vs 39%) were also pronounced (Figure S2; Figure 2).

Discussion

This post hoc analysis builds on the primary findings of the SYNAPSE study, which demonstrated the therapeutic benefits of mepolizumab versus placebo for patients with severe, recurrent, refractory CRSwNP. The results presented here demonstrate that patients without sinus surgery during SYNAPSE experienced more clinical improvements with mepolizumab than standard of care plus placebo, based on five clinically relevant criteria representing disease-specific QoL, NP size, nasal obstruction, loss of smell, and overall symptoms [4, 28]. The majority of patients without surgery treated with mepolizumab (~90%) showed clinical improvement in ≥1 response criterion at Weeks 24 and 52. Moreover, clinical improvements increased over time from Week 24 to Week 52, with approximately half of patients treated with mepolizumab having clinical improvements in at least three

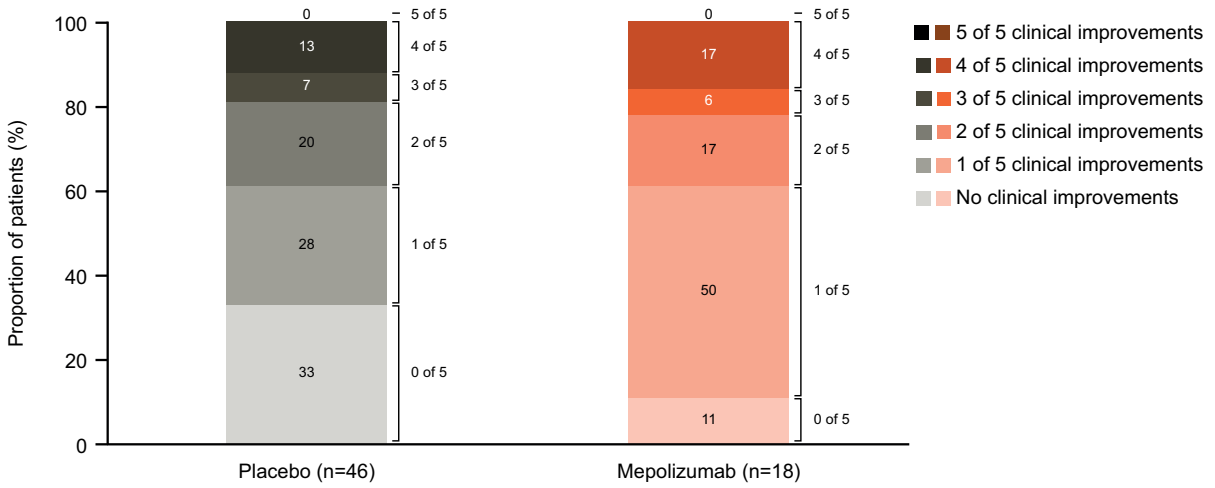

Figure 5. Surgery subgroup: Proportion of responders by number of clinical improvements*. Data are from patients' last visit before surgery; *Defined as improvement in: a) SNOT-22 total score (≥8.9-point); b) total endoscopic nasal polyp score (≥1-point); c) nasal obstruction VAS score (≥3-point); d) loss of smell VAS score (≥3-point); e) overall symptoms VAS score (≥2.5- point). SNOT-22, sinonasal outcome test-22; VAS, visual analog scale.

criteria at Week 24 and two-thirds of patients at Week 52. Together, these results suggest a sustained and progressive response to mepolizumab in patients with severe CRSwNP. The trends described here were also seen in the subgroup of patients with neither surgery nor SCS use during the study.

Our analysis did not reveal any clear differences in baseline characteristics between the one-quarter of patients treated with mepolizumab who met all five response criteria and the smaller minority of non-responders at Week 52. Although baseline blood eosinophil counts were numerically lower for full-responders than non-responders across mepolizumab and placebo groups, baseline blood eosinophil counts were still >300 cells/μL for both full- and non-responders treated with mepolizumab, at Weeks 24 and 52. Overall, this suggests further investigation is needed to understand why some patients with CRSwNP achieve a wide range of clinical improvements while some have no improvements. Furthermore, this highlights the unmet need for predictive biomarkers to identify which patients with CRSwNP are most likely to benefit from targeted biologic treatment [14]. Currently, mepolizumab (targeting free IL-5), dupilumab (targeting IL-4 and IL-13 signaling), and omalizumab (targeting free IgE) have been approved for CRSwNP treatment following supportive clinical efficacy data from Phase III trials [15-18]. Identifying predictive biomarkers and differences in optimal target populations will be important for further delineation of treatment algorithms.

Our results showed that the proportion of patients with clinical benefit based on each of the five individual response criteria was higher with mepolizumab versus placebo at both Week 24 and Week 52 for both the no surgery and neither surgery nor SCS subgroups. The most commonly observed benefits were in SNOT-22 score, overall symptoms VAS score, and nasal obstruction VAS score. Improvements were also seen in loss of smell, which is often poor in patients who have undergone previous sinus surgery for NP [29, 30]. Improved loss of smell, therefore, represents an important outcome in the SYNAPSE population, who had all undergone sinus surgery prior to enrollment, especially given the association between loss of smell and worse disease-specific QoL [31]. As the proportion of patients with improvements in each individual criterion generally increased over time from Weeks 24 to 52, these results suggest that sufficient time should be permitted to determine which patients may achieve clinical benefit with mepolizumab. Interestingly, the proportion of patients meeting the SNOT-22 criterion (≥8.9-point improvement from baseline) was similar at Weeks 24 and 52 (~80%), which might suggest improvements in disease-specific QoL with mepolizumab are achieved earlier during treatment compared with the other benefits. The high proportion of mepolizumab-treated patients achieving a meaningful response in SNOT-22 score may also reflect the modest 8.9-point minimum clinically important difference (MCID) for SNOT-22 compared with the approximately 30-point improvement in mean change from baseline to Week 52 of the SYNAPSE study [15, 32]. This response is similar to that observed with the T2-targeting monoclonal antibody dupilumab in patients with CRSwNP [18].

Our analysis suggests that SCS use did not impact the results, since the results were similar between the no surgery subgroup and the neither surgery nor SCS use subgroup. This is despite patients on placebo receiving approximately twice as much SCS during SYNAPSE than patients receiving mepolizumab (181 vs 109 mg/patient/year respectively) [15]. These results also suggest that SCS use did not contribute to the placebo effect observed. Therefore, the clinical responses observed for patients in the placebo group (also observed in other trials of biologics in

CRSwNP [16, 18]) may in part be attributed to increased compliance with intranasal corticosteroids as part of standard of care. While parallel changes in patient behavior would also be expected in the mepolizumab group, this contribution to improvement does not detract from the demonstrated benefits of mepolizumab beyond those seen with placebo.

As expected, having surgery affected the number of clinical improvements. While the SNOT-22 response was similar for patients treated with mepolizumab with and without surgery, far fewer patients who required surgery achieved responses in the other four criteria, compared to patients without surgery. As the majority of surgeries performed during the study occurred after Week 24, this suggests that patients and treating physicians, who were blinded to the treatment arm, may have waited for 6 months to assess treatment effects before deciding whether to proceed to surgery.

Interpretation of these post hoc analyses should be placed in the context of the confirmed benefits of mepolizumab over standard of care alone in patients with severe CRSwNP. Here we examined the clinical benefits for patients who had no surgery (or SCS use) during the study, despite a prior history of surgery and a need for repeat surgery at enrollment in SYNAPSE. The previously demonstrated clinical benefits of mepolizumab versus placebo in SYNAPSE included a significant reduction in the risk of undergoing further surgery and the odds of a patient requiring SCS [15]. Our results build on this and provide evidence that mepolizumab continued to provide clinically meaningful improvements in disease-specific QoL, NP size, nasal obstruction, sense of smell and overall symptoms over standard of care alone in patients who no longer required repeated surgery after initiating mepolizumab treatment.

General limitations of the study design of SYNAPSE have previously been discussed and include the subjective nature of the physician decision to proceed to surgery or prescribe SCS based on assessment of clinical need [15]. In the context of post hoc analyses, small patient numbers can be expected in some subgroups. Furthermore, this post hoc analysis was not powered for significance testing and, therefore, only descriptive analyses were performed. Notably, for the comparison of baseline characteristics between non- and full-responder subgroups, responders were defined based on the number of response criteria met, as per the proposal for defining response to biological treatment in the EUFOREA guidelines [4]. We acknowledge that this approach assumes some equivalency of the five different response criteria, which may not be accurate for all patients, with some likely feeling that response in one category is more 'clinically meaningful' than response in another. Indeed, the relative importance of these five criteria to patients has not yet been established. Additionally, patients who had surgery during SYNAPSE were excluded from the comparison of baseline characteristics for non- versus full responders. This approach may have reduced any differences between non- and full responder groups, as the surgery subgroup had a high proportion of non-responders, especially in the placebo arm. Additionally, the decision to perform surgery is multifactorial and can vary between countries and regionally even within a country. For instance, a retrospective study of sinus surgeries performed in Finland found a four-fold regional variation in surgery rates that was independent of patient age and gender [33]. Furthermore, differences in post-operative care can result in heterogenous outcomes [34]. Therefore, as all patients enrolled in SYNAPSE had undergone at least one previous surgery (within 10 years of enrollment), the individual potential of patients to achieve clinically meaningful improvements with mepolizumab may have varied. Additionally, as computed tomography scanning was not performed at baseline, it is not possible to determine if there were differences in the type and surgical completeness of prior surgery, which may have also affected patient outcomes.

Conclusion

In conclusion, this post hoc analysis of SYNAPSE demonstrated that there were no clear differences in baseline characteristics between patients considered to be non-responders to mepolizumab treatment and those considered to be full responders, highlighting a need for further investigation of biomarkers that may predict response to treatment. Patients who did not have sinus surgery during the study and those who neither had sinus surgery nor SCS continued to achieve a sustained and progressive response to mepolizumab, based on several clinically relevant criteria. Taken together, these results provide further evidence of the therapeutic benefit of mepolizumab in a population of patients with severe, recurrent, refractory, bilateral CRSwNP, who have a prior history of NP surgery, and who demonstrated a current need for repeat sinus surgery at enrollment.

Authorship contribution

ARS, JM, BM, SWY and RC were involved in study conception or design. CH, JH, CB, WJF, and SEL were involved in the acquisition of data. ARS, BM, SWY, RC, CH, JH, CB, WJF, SEL, and JM contributed to data analysis or interpretation. All authors were involved in drafting the work and/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

CH has received advisory board fees from Sanofi, AstraZeneca, Olympus, and GSK, and lecture fees from Mylan; JKH has received consultancy fees from Sanofi-Genzyme-Regeneron, Genentech, AstraZeneca, GSK, and Gossamer Bio; VJL reports advisory board and/or lecture fees from Sanofi, Novartis, GSK, Abbot and Medscape; CB has participated in advisory boards and received speaker fees from ALK-Abello, AstraZeneca, Sanofi, Novartis, GSK, and Meda Pharmaceuticals; WJF has received clinical trial funding from Sanofi, Mylan, ALK-Abelló, Allergy Therapeutics, Novartis, and Chordate, and personal fees from Sanofi, GSK, and Lyra; ZD has acted as Research Director at QPS-NL, an institution for clinical drug development, which received research support from several bio-pharmaceutical companies (HAL Allergy, Foresee Pharmaceuticals, Patara Pharma (now Respivant), and Novartis), and has also received, speaker fees, advisory board fees or consultancy fees from ALK, AstraZeneca, Antabio, Boehringer Ingelheim, GSK, HAL Allergy, Merck Sharp & Dohme, Sanofi-Genzyme-Regeneron, all outside the submitted work; JM has participated in advisory boards for, received research grants from, or participated in speakers' bureaus for AstraZeneca, Genentech, GSK, Glenmark, Menarini, Mitsubishi-Tanabe Pharma, MSD, Viatris (Mylan-Meda Pharmaceuticals), Novartis, Proctor & Gamble, Regeneron Pharmaceuticals, Sanofi-Genzyme, UCB Pharma, and Uriach Group, and has received clinical trial funding or research grants from AstraZeneca, Genentech, GSK, MSD, Novartis, Regeneron Pharmaceuticals, Sanofi-Genzyme, Viatris (Mylan-Meda Pharmaceuticals), and Uriach Group; ARS, SGS, SY, BM, and RHC are employees of GSK and own stocks/shares in GSK; SWY was an employee of GSK at the time of the analysis and owns stocks/shares in GSK; SEL has participated in advisory boards and received clinical trial funding from Sanofi-Genzyme-Regeneron, Genentech, AstraZeneca, and GSK.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Table S1. Demographics and baseline characteristics in patients with and without surgery prior to Week 52.

	Placebo		Mepolizumab	
	Patients without surgery prior to Week 52 (n=155)	Patients with surgery prior to Week 52(n=46)	Patients without surgery prior to Week 52 (n=188)	Patients with surgery prior to Week 52 (n=18)
Age, years, mean (SD)	49.1 (13.00)	48.2 (10.55)	48.8 (13.60)	47.1 (13.28)
Female, n (%)	58 (37)	18 (39)	64 (34)	3 (17)
Duration of CRSwNP, years, mean (SD)	11.5 (8.57)	11.5 (7.26)	11.02 (8.28)	14.9 (10.35)
Blood eosinophil count, cells/µL, geometric mean (SD logs)	380 (0.762)	450 (0.814)	390 (0.763)	380 (0.692)
Comorbid conditions, n (%)				
Asthma	117 (75)	32 (70)	125 (66)	15 (83)
AERD/N-ERD	45 (29)	18 (39)	40 (21)	5 (28)
Allergic Rhinitis	85 (55)	20 (43)	107 (57)	7 (39)
SNOT-22 total score (0-110), mean (SD)	n=153 64.0 (18.51)	n=45 66.0 (20.89)	n=187 63.8 (17.62)	n=18 62.2 (18.24)
Total endoscopic NP score (0-8, centrally read), mean (SD)	5.3 (1.35)	6.5 (1.21)	5.3 (1.15)	6.1 (1.21)
VAS score (0-10), mean (SD)				
Nasal obstruction	9.0 (0.86)	9.3 (0.67)	8.9 (0.84)	9.3 (0.72)
Loss of smell	9.6 (0.63)	9.8 (0.45)	9.6 (0.85)	9.7 (0.56)
Overall symptom	9.1 (0.74)	9.3 (0.63)	9.0 (0.77)	9.2 (0.74)
Composite – nasal symptoms	9.0 (0.84)	9.2 (0.82)	8.9 (0.80)	9.2 (0.79)
Time since most recent CRSwNP surgery, years mean (SD)	n=154 3.8 (2.72)	n=46 3.8 (2.57)	n=187 4.1 (2.61)	n=18 5.4 (3.17)
Patients with ≥1 course of SCS for CRSwNP in the previous 12 months, n (%)	66 (43)	25 (54)	97 (52)	9 (50)

AERD, aspirin-exacerbated respiratory disease; N-ERD, nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease; NP, nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; SCS, systemic corticosteroids; SD, standard deviation; SNOT-22, sinonasal outcome test-22; VAS, visual analog scale.

Table S2. Proportion of responders in patients with no surgery, and with neither surgery nor SCS use prior to Weeks 24 and 52.

Number of response criteria met	Patients with no surgery at Week 24		Patients with no surgery at Week 52	
	Response at Week 24, n (%)		Response at Week 52, n (%)	
	Placebo (n=183)	Mepolizumab (n=198)	Placebo (n=155)	Mepolizumab (n=188)
0 clinical improvements*	37 (20)	16 (8)	32 (21)	26 (14)
≥1 of 5 clinical improvements*	146 (80)	182 (92)	123 (79)	162 (86)
≥2 of 5 clinical improvements*	90 (49)	141 (71)	91 (59)	143 (76)
≥3 of 5 clinical improvements*	64 (35)	109 (55)	76 (49)	126 (67)
≥4 of 5 clinical improvements*	32 (17)	71 (36)	47 (30)	105 (56)
5 of 5 clinical improvements*	5 (3)	24 (12)	16 (10)	47 (25)
Number of response criteria met	**Patients with neither surgery nor SCS use at Week 24**		**Patients with neither surgery nor SCS use at Week 52**	
	Response at Week 24, n (%)		Response at Week 52, n (%)	
	Placebo (n=150)	Mepolizumab (n=165)	Placebo (n=117)	Mepolizumab (n=149)
0 clinical improvements	27 (18)	11 (7)	24 (21)	19 (13)
≥1 of 5 clinical improvements*	123 (82)	154 (93)	93 (79)	130 (87)
≥2 of 5 clinical improvements*	79 (53)	122 (74)	69 (59)	115 (77)
≥3 of 5 clinical improvements*	58 (39)	96 (58)	59 (50)	102 (68)
≥4 of 5 clinical improvements*	26 (17)	62 (38)	35 (30)	87 (58)
5 of 5 clinical improvements*	4 (3)	23 (14)	13 (11)	43 (29)

*Defined as improvement from baseline in: a) SNOT-22 total score (≥8.9-point); b) total endoscopic nasal polyp score (≥1-point); c) nasal obstruction VAS score (≥3-point); d) loss of smell VAS score (≥3-point); or e) overall symptoms VAS score (≥-2.5-point). SCS, systemic corticosteroids; SNOT-22, sinonasal outcome test-22; VAS, visual analog scale.

Table S3. Proportion of responders in patients with surgery prior to Week 52, at most recent visit before surgery.

Number of response criteria met	Patients with surgery by Week 52	
	Response at Week 52, n (%)	
	Placebo (n=46)	Mepolizumab (n=18)
0 clinical improvements*	15 (33)	2 (11)
≥1 of 5 clinical improvements*	31 (67)	16 (89)
≥2 of 5 clinical improvements*	18 (39)	7 (39)
≥3 of 5 clinical improvements*	9 (20)	4 (22)
≥4 of 5 clinical improvements*	6 (13)	3 (17)
5 of 5 clinical improvements*	0	0

*Defined as improvement from baseline at patients' last study visit prior to surgery in: a) SNOT-22 total score (≥8.9-point); b) total endoscopic NP score (≥1-point); c) nasal obstruction VAS score (≥3-point); d) loss of smell VAS score (≥3-point); or e) overall symptoms VAS score (≥-2.5-point). NP, nasal polyps; SCS, systemic corticosteroids; SD, standard deviation; SNOT-22, sinonasal outcome test-22; VAS, visual analog scale.

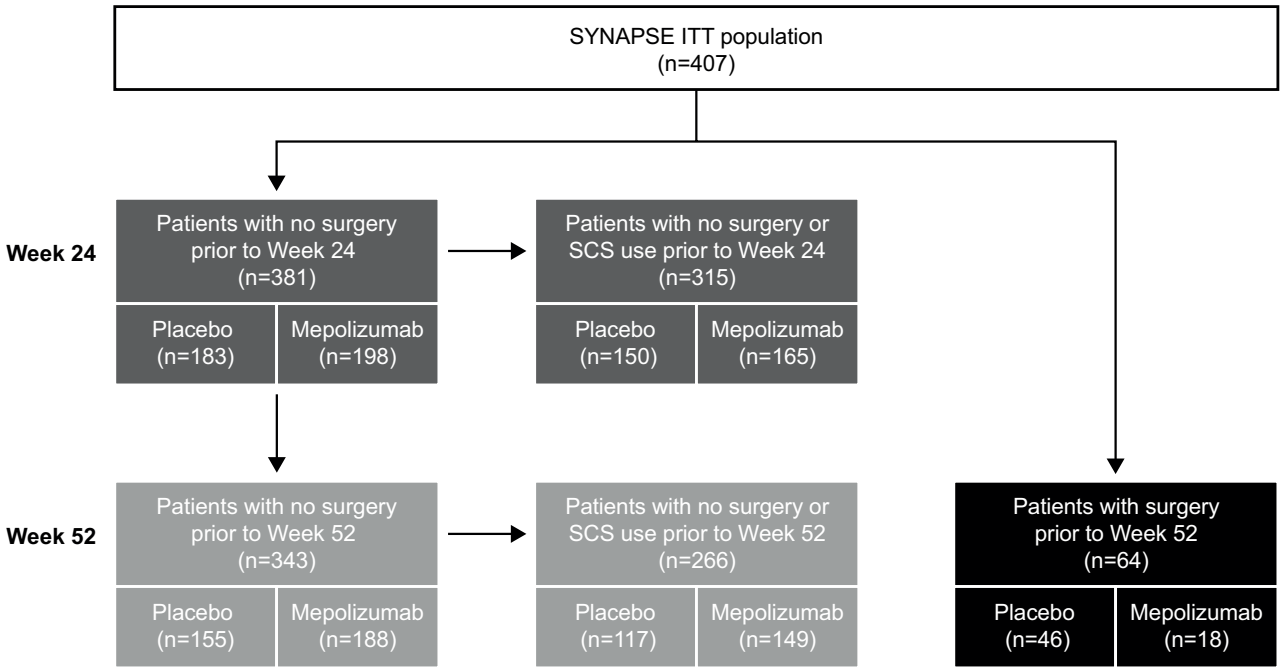

Figure S1. Subgroups included in the post hoc analysis.

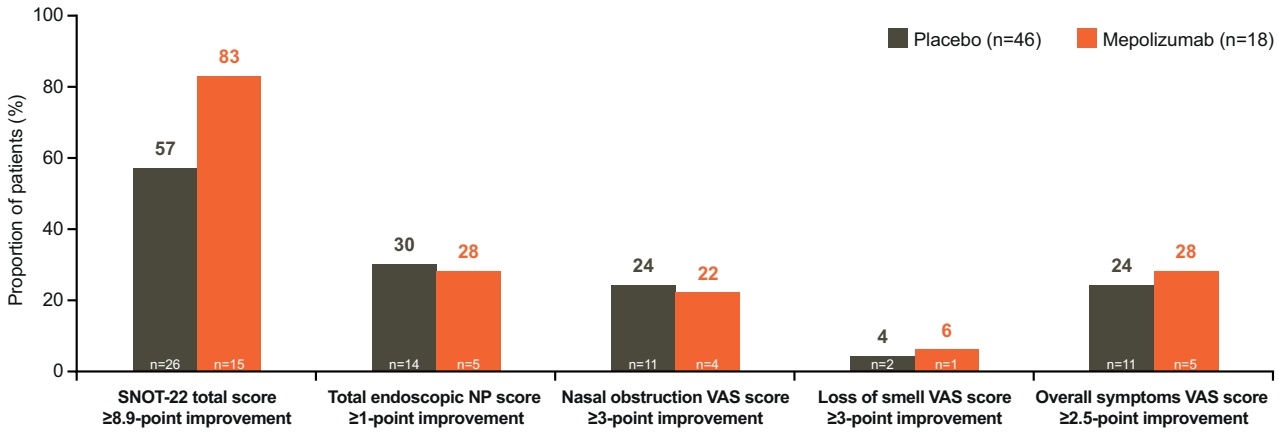

Figure S2. Surgery subgroup: proportion of responders by individual responder criteria among patients who went on to have surgery by Week 52. Data from patients' last clinical visit before surgery were used. NP, nasal polyps; SNOT-22, sinonasal outcome test-22; VAS, visual analog scale.