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Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): in-depth sinus surgery analysis

(99/<100 characters)

Running title: SYNAPSE CRSwNP surgery need after mepolizumab

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Abstract (243/250 words)

Background

Patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP) often require repeat sinus surgery. Mepolizumab reduced the need for sinus surgery in the SYNAPSE trial; this analysis sought to provide a more in-depth assessment of surgery endpoints in SYNAPSE.

Methods

SYNAPSE was a double-blind Phase III trial (NCT03085797) in adults with recurrent, refractory, severe, CRSwNP eligible for repeat sinus surgery despite standard of care treatments and previous surgery. Patients were randomized (1:1) to mepolizumab 100 mg subcutaneously or placebo, plus standard of care, every 4 weeks for 52 weeks. Time to first inclusion on a waiting list for sinus surgery and time to first actual sinus surgery (both up to Week 52) were assessed; the latter endpoint was also analysed post hoc according to time since last sinus surgery before study screening and baseline blood eosinophil count.

Results

Among 407 patients (mepolizumab: 206; placebo: 201), mepolizumab versus placebo reduced the risk of being included on a waiting list for sinus surgery (Week 52 Kaplan-Meier probability estimate [95% confidence interval]: 13.9% [9.8%, 19.5%] vs 28.5% [22.7%, 35.4%]). Mepolizumab versus placebo reduced the risk of sinus surgery irrespective of time (<3 vs ≥3 years) since patients' last sinus surgery prior to study screening (hazard ratios [95% confidence intervals] 0.28 [0.09, 0.84] and 0.50 [0.26, 0.98], respectively) and baseline blood eosinophil count.

Conclusions

Mepolizumab reduced the risk of further sinus surgery in patients with recurrent, refractory, severe CRSwNP, irrespective of the patient baseline characteristics assessed.

Keywords: chronic rhinosinusitis with nasal polyps, mepolizumab, recurrence, refractory, sinonasal surgery

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a phenotype of CRS characterized by the presence of NP, the most common endotype of which is chronic local eosinophilic inflammation, with interleukin (IL)-5 and type 2 inflammation playing a key underlying role in its pathophysiology.[1-5] The 2020 European Position Paper on Rhinosinusitis and Nasal Polyps defines CRSwNP as the presence of two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), with or without facial pain/pressure and/or a reduction in or loss of smell for ≥12 weeks, in addition to endoscopic confirmation of NP in the middle meatus.[6] Patients with CRSwNP can experience these symptoms over many years, leading to a substantial negative impact on numerous aspects of health-related quality of life including physical health, mental health, social functioning and sleep.[7-11]

Current standard of care for CRSwNP includes intranasal corticosteroids, saline nasal douching and short courses of systemic corticosteroids (SCS), the latter of which are associated with dose- and time-dependant potential serious adverse side effects.[6,12,13] For severe cases of CRSwNP, sinus surgery to remove the NP tissue and diseased nasal mucosa is often required.[6] However, surgery can be associated with complications such as bleeding, orbital injury, and cerebrospinal fluid leak.[14] Moreover, the postoperative recurrence of NP can vary based on a patient's background medications, comorbidities, allergic sensitisation, non-steroidal anti-inflammatory drug intolerance and disease severity (as indicated by the number of previous surgeries and/or blood eosinophil count).[15-19] Repeat sinus surgery is associated with diminishing success and a higher potential for permanent damage/scarring of the nasal mucosa[16,20,21] which, coupled with the prolonged inflammation associated with recurring NP, can lead to a loss of sense of smell.[22,23] Significant predictors of revision surgery include eosinophilic disease, comorbid allergic sensitization and elevated IL-5 in the nasal mucosa.[15,18,24,25]

Mepolizumab is a humanized monoclonal antibody that binds to and inactivates IL-5, the major cytokine responsible for the proliferation, activation and survival of eosinophils.[26-28] Mepolizumab is approved for the treatment of several eosinophilic diseases in multiple regions worldwide. These include severe eosinophilic asthma, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome and CRSwNP.[29,30] Phase II studies have shown

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that mepolizumab reduces the need for sinus surgery in patients with severe CRSwNP, in addition to reducing NP size and improving symptoms, compared with placebo.[31,32] In the Phase III SYNAPSE study, patients with severe CRSwNP with at least one prior sinus surgery and in need of revision surgery demonstrated significant improvements from baseline in total endoscopic NP score (NPS) and nasal obstruction Visual Analogue Scale (VAS) score, in addition to other symptom endpoints, with mepolizumab versus placebo.[33] ENREF 18 Patients also demonstrated a reduced risk and need for surgery with mepolizumab versus placebo.[33] This analysis of the SYNAPSE study aimed to provide a more in-depth assessment of the impact of mepolizumab on surgery endpoints in patients from SYNAPSE with recurrent severe CRSwNP despite current optimal medical management and prior sinus surgery.

Methods

Study design

The study design and eligibility criteria of SYNAPSE have been previously described.[33] Briefly, SYNAPSE was a Phase III, randomized, double-blind, placebo-controlled, parallel-group trial (GSK ID: 205687; NCT03085797). Patients were randomized (1:1) to receive 4-weekly mepolizumab 100 mg or placebo subcutaneously using a pre-filled safety syringe, in addition to standard of care treatment, for 52 weeks. Standard of care included daily mometasone furoate nasal spray (200 or 400 µg/day) throughout the study period, in addition to saline nasal irrigations, and courses of SCS and/or antibiotics, as required. 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/.

*When reporting VAS outcomes in this study, patients quantified the severity of their symptoms on an electronic device that 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).

Patients

Eligible patients were adults with bilateral CRSwNP as diagnosed by nasal endoscopy, with recurrent, refractory, severe sinonasal symptoms (nasal obstruction symptom VAS score* of >5 [scale 0–10]) who were eligible for repeat sinus surgery (overall symptoms VAS score >7 and a total endoscopic NPS ≥5 [scale 0–8], with a minimum score of 2 in each nasal cavity), despite standard of care treatment. Patients had to have had at least one sinus surgery (defined as any surgery of the paranasal sinuses with resulting nasal polypectomy) within the last 10 years. Eligible patients also required stable maintenance therapy with intranasal spray medication (mometasone furoate) for ≥8 weeks before screening and displayed ≥2 symptoms including nasal blockage/obstruction/congestion and/or nasal discharge (anterior or posterior nasal drip) for ≥12 weeks before screening, with facial pain or pressure and/or a reduction in or loss of sense of smell. Patients with antrochoanal polyps, nasal septal deviation occluding one nostril, rhinitis medicamentosa, any intranasal and/or sinus surgery in the 6 months before screening, or a contraindication for sinus surgery in the opinion of the Investigator were excluded.

Endpoints

The co-primary and secondary endpoints from the SYNAPSE study have been previously reported.[33] This manuscript focuses on an in-depth analysis of the surgery endpoints of the study, listed in **Supplementary Table 1**. Previously reported SYNAPSE surgery endpoints included the proportion of patients no longer having a need for sinus surgery (defined as an overall symptom VAS score ≤7 [Weeks 49–52] and a total endoscopic NPS <5 [Week 52]), the proportion of patients with ≥1 sinus surgery during the study period, time to first sinus surgery up to Week 52 (following study initiation), and the crude annualized rate of sinus surgeries.[33] To further assess the need for sinus surgery during SYNAPSE, additional surgery endpoints reported here include the proportion of patients on a waiting list for sinus surgery during the study period and time to first inclusion on a waiting list for sinus surgery (following study initiation) up to Week 52. With regards to actual sinus surgeries, the proportion of patients with 1 and 2 surgeries during the study period and the types of procedures performed were described.

To assess the impact of time since a patient's last sinus surgery on NP severity and subsequent surgeries, post hoc subgroup analyses were performed in patients stratified by time since last surgery before study screening (<3 vs ≥3 years; based on the results of previous surgery recency analyses in patients with CRSwNP receiving biologic treatment[34]).

The outcomes included in these analyses were the time to first sinus surgery up to Week 52 and the proportion of patients with: a >1-point improvement from baseline to Week 52 in total endoscopic NPS; a >1-point improvement from baseline to Weeks 49–52 in nasal obstruction VAS score; a sinus surgery during the study. When reporting VAS in this study, patients quantified the severity of their symptoms on an electronic device which represented the 0–10 cm paper scale, with 0 conferring total absence of symptom(s) and 10 conferring the worst thinkable severity of symptom(s).

To assess whether other patient baseline characteristics were associated with an increased need for sinus surgery, descriptive statistics were provided for: the mean time since patients' last sinus surgery (years), the proportion of patients with 1, 2 or ≥3 sinus surgeries before study screening, and $\log_e$ baseline blood eosinophil count (cells/μL), by the presence/absence of sinus surgeries during the study treatment period (0 vs ≥1 surgeries); mean time since last sinus surgery prior to study screening (years), by $\log_e$ baseline blood eosinophil count categories (<300, ≥300, <150 and ≥150 cells/μL).

Statistical analysis

All endpoints were assessed in randomized patients who received ≥1 dose of study drug (intent-to-treat [ITT] population). Time to inclusion on a waiting list for sinus surgery and time to first sinus surgery were analysed using a Cox proportional hazards model with covariates of treatment group, baseline total endoscopic NPS (centrally read), baseline nasal obstruction VAS score, geometric mean baseline blood eosinophil count, number of previous sinus surgeries (1, 2, or ≥3; ordinal) and geographical region. The proportion of patients no longer needing sinus surgery was analysed using a logistic regression model with covariates of treatment group, baseline NPS (centrally read), baseline nasal obstruction VAS score, geometric mean baseline blood eosinophil count and geographical region. As previously described,[33] all data up to Week 52 were included in the analyses regardless of treatment discontinuation. All data were analysed using Statistical Analysis Software (SAS; version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Patient population

A total of 407 patients (206 receiving mepolizumab, 201 receiving placebo) received ≥1 dose of study drug and were included in the analyses; 373 patients (184 receiving mepolizumab and 189 receiving placebo) completed study assessments to Week 52. Baseline

characteristics have been reported previously by treatment group[33] and are shown overall and for patients with their last sinus surgery <3 and ≥3 years before study screening in **Table 1**. Prior to study screening, all patients had undergone ≥1 previous sinus surgery as per the inclusion criteria, with 54% (n=218/407) and 31% (n=124/407) of patients having had ≥2 and ≥3 previous sinus surgeries, respectively. As expected, patients with their last sinus surgery ≥3 versus <3 years before screening had a longer duration of NP and a longer time since their previous sinus surgery (**Table 1**); all other characteristics were similar across these two subgroups.

Sinus surgery outcomes

The proportion of patients identified as no longer needing sinus surgery has been reported previously[33] and was significantly higher in the mepolizumab group (72% [n=149/206]) than in the placebo group (51% [n=103/201]) (**Table 2**). The proportion of patients who had been placed on a waiting list for sinus surgery during the 52-week treatment period was lower in the mepolizumab (16% [n=33/206]) versus placebo (30% [n=60/210]) group (**Table 2**). Consequently, patients treated with mepolizumab had a significantly lower estimated risk of being included on a waiting list for sinus surgery prior to Week 52 than those in the placebo group (**Figure 1, Table 2**).

In total, 9% (n=18/206) of mepolizumab-treated and 23% (n=46/201) of placebo-treated patients had ≥1 sinus surgery during the 52-week study period (**Table 2**);[33] 8% (n=16/206) and 21% (n=43/201), respectively, had 1 sinus surgery while <1% (n=2/206) and 1% (n=3/201), respectively, had 2 sinus surgeries. Among the 69 surgeries reported (20 in the mepolizumab group and 49 in the placebo group), 46 (11 in the mepolizumab group and 35 in the placebo group) were procedures identified as functional endoscopic sinus surgery (FESS) and 23 (9 in the mepolizumab group and 14 in the placebo group) were procedures identified as nasal polypectomies (**Table 2**). The crude annualized sinus surgery rate has been previously reported,[33] and was 0.10 versus 0.25 events/year in the mepolizumab and placebo groups, respectively (**Table 2**).

Impact of time since last sinus surgery on NP severity and subsequent surgeries

A greater proportion of patients experienced >1-point improvements in total endoscopic NPS up to Week 52 with mepolizumab versus placebo, irrespective of whether their last sinus surgery was <3 or ≥3 years before study screening (**Figure 2**). This finding was also observed for the proportion of patients experiencing >1-point improvements in nasal

obstruction VAS score up to Weeks 49–52 (**Figure 2**). In both treatment groups, a numerically higher proportion of patients with their last sinus surgery ≥3 years before screening had sinus surgery during the 52-week treatment period, compared with those whose last surgery was <3 years before screening (**Figure 3**). Moreover, patients with their last sinus surgery <3 years before screening demonstrated numerically greater reductions in the risk of sinus surgery with mepolizumab versus placebo than patients with sinus surgery ≥3 years before screening (**Figure 4**). In the mepolizumab group, patients with sinus surgeries during the study period had a longer time since their most recent surgery prior to study screening (5.4 years), compared with those without sinus surgeries (4.1 years). Conversely, in the placebo group, the mean time since last surgery was the same (3.8 years) for patients with and without sinus surgeries during the study.

Impact of other patient characteristics on the need for sinus surgery

In both treatment groups, more patients with sinus surgeries during the 52-week study period than those without had 3 or more sinus surgeries before the study (**Figure 5**). Baseline blood eosinophil counts were generally similar among patients with and without sinus surgeries during the study (geometric mean [standard deviation logs] baseline blood eosinophil counts: 380 [0.69] vs 390 [0.76] cells/μL for patients with vs without sinus surgeries in the mepolizumab group; 450 [0.81] vs 380 [0.76] cells/μL for patients with vs without sinus surgeries in the placebo group). However, in both treatment arms combined, patients who received sinus surgery during the study had higher baseline blood eosinophil counts than those who didn't (430 [0.78] vs 390 [0.76] cells/μL for patients with vs without sinus surgeries). Although no clear associations were observed between baseline blood eosinophil count and the time since last sinus surgery before study screening, patients with a baseline blood eosinophil count ≥300 cells/μL had a shorter time since their most recent sinus surgery than those with lower blood eosinophil counts (mean time since last surgery: 4.1, 4.0, 4.3 and 3.9 years in patients with blood eosinophil counts <150, ≥150, <300 and ≥300 cells/μL, respectively).

Discussion

Among the SYNAPSE patient population, treatment with mepolizumab has been previously shown to reduce the risk of sinus surgery versus placebo and lead to a higher proportion of patients no longer needing sinus surgery by study end.[33] Although sinus surgery is an important treatment option for patients with CRSwNP, undergoing repeat surgeries with occasionally only temporary or unpredictable outcomes and potentially long recovery times

is a concern for patients.[35] Repeat surgeries are also associated with increased overall clinical burden (including healthcare resource utilisation and costs).[36] It was therefore important to perform a further in-depth assessment of the effect of mepolizumab on sinus surgery endpoints. Our secondary analyses showed that the risk of being placed on a waiting list for sinus surgery during the 52-week treatment period was lower in the mepolizumab group than in the placebo group, thus supporting previous SYNAPSE findings when capturing those patients who were eligible for but had not yet undergone repeat sinus surgery during the study period. They also demonstrated that even in those patients who had not undergone sinus surgery in several years, mepolizumab was more effective than placebo at improving NP symptoms and reducing the proportion of patients who required sinus surgery. Together these data further support the clinically important benefits of mepolizumab in reducing the need for and incidence of sinus surgery in patients with severe CRSwNP. The importance of these findings is emphasized by the diminishing success of repeat sinus surgery, in addition to the higher potential for permanent damage/scarring.[20,21]

In addition to reducing the risk of undergoing sinus surgery or being placed on a waiting list for sinus surgery during SYNAPSE, mepolizumab was associated with a reduction in the need for sinus surgery as defined by overall symptom VAS score and total endoscopic NPS.[33] All patients were identified as needing sinus surgery at study initiation; after 52 weeks of treatment, over two-thirds of patients receiving mepolizumab no longer needed sinus surgery compared with approximately half of patients receiving placebo. The improvements in the placebo group may be due to increased compliance with standard of care (intranasal corticosteroid) therapy as part of the study. Of note, a higher proportion of patients in the placebo group required SCS during the study period than in the mepolizumab group (37% vs 25%).[33] SYNAPSE patients receiving placebo also received higher SCS doses during the treatment period than those receiving mepolizumab (mean prednisolone-equivalent 181 vs 109 mg/year).[33] Since SCS use is likely to have reduced the symptom scores used to define a need for sinus surgery, it is possible that on-treatment SCS use contributed to the proportion of patients in the placebo group who were later identified as no longer needing sinus surgery at the end of the study. This effect of SCS is also an important consideration in clinical practice; those patients receiving SCS treatment may not have overall symptom and total endoscopic NPS indicative of a need for sinus surgery but may still experience clinical benefits with biologic treatment, particularly given the serious side effects associated with long-term SCS use.[12] A multitude of factors may impact whether a patient is prescribed SCS,

limited versus extended sinus surgery, or biologic treatment. These include (but are not limited to) disease severity, comorbidities, risk of polyp recurrence, resource availability and costs, safety, surgeon/physician preferences and patient preferences and goals.[37,38]

Contrary to previous studies of biologic treatment in patients with severe CRSwNP,[34] we did not observe a trend towards larger treatment effect among patients whose last surgery was <3 years before screening versus ≥3 years before screening. Instead, the proportions of mepolizumab-treated patients with improved total endoscopic NPS were similar irrespective of the recency of sinus surgery.

To determine whether particular patient characteristics are associated with an increased need for sinus surgery, we also described some of the baseline attributes of patients who had sinus surgery during the study compared with those who did not have surgery. Those who underwent sinus surgery during SYNAPSE had a history of more frequent surgeries and had a longer time since their most recent sinus surgery prior to study initiation. Interestingly, the mean time since patients' most recent sinus surgery prior to study initiation did not appear to be related to baseline blood eosinophil count. However, a number of previous studies have shown higher rates of NP recurrence following sinus surgery in those with higher versus lower blood or tissue eosinophils.[25,39] Our previous subgroup analysis of the co-primary endpoints in SYNAPSE suggested that the efficacy of mepolizumab is higher with higher baseline blood eosinophil counts.[33] Conversely, a small study in patients receiving dexpramipexole for the treatment of CRSwNP showed that treatment-induced reductions in both blood and tissue eosinophils were not associated with significant reductions in total endoscopic NPS.[40] Although the role of blood eosinophils in predicting disease prognosis and response to treatment is well established in severe eosinophilic asthma,[27] this relationship has not yet been clearly demonstrated in patients with severe CRSwNP. While the role of blood eosinophil count in predicting NP recurrence and need for surgery therefore requires further investigation, it is plausible that since the eligibility criteria for SYNAPSE resulted in a study population of patients with very severe CRSwNP, blood eosinophil count may not be a particularly sensitive indicator of NP recurrence among these patients.

There were a number of limitations to the SYNAPSE study, as previously described. ENREF 19[33] Briefly, if a patient met the criteria for surgery during the study, the decision to prescribe another course of SCS or proceed to surgery was decided by the physician. Physicians would have been influenced by many subjective factors beyond severity, including surgeon preference, patient desire, and comorbidities. The order in which

investigating physicians prescribed SCS, a simple polypectomy or more extensive sinus surgery was not recorded during SYNAPSE; future real-world studies to further assess physicians' decision-making processes and how these impact patient treatment pathways would therefore be useful. Additionally, because the type of sinus surgery (e.g., simple polypectomy vs endoscopic sinus surgery vs extended surgery) can affect the risk of NP recurrence, the types of previous sinus surgery received could have influenced surgery decisions; these factors were largely controlled for because the patients were randomly assigned to treatment. Furthermore, some of the subgroup analyses included groups with small numbers of patients and should be interpreted with caution. Finally, eligibility for repeat sinus surgery in this study was defined as and overall symptoms VAS score >7 and a total endoscopic NPS ≥5 (minimum score of 2 in each nasal cavity) and this has not been fully validated in patients with CRSwNP. Nonetheless, the surgery endpoints from this Phase III study showed the efficacy of mepolizumab in reducing both the need for sinus surgeries and actual sinus surgeries in adults with severe CRSwNP.

In conclusion, mepolizumab reduced the need for and the incidence of sinus surgeries in adult patients who have recurrent severe CRSwNP despite current medical management and prior sinus surgery. As such, mepolizumab represents an important treatment option for these patients who have a substantial burden of disease.

Author contributions

WJF, RCK, ARS, VSB, BM, SWY and RC contributed to conception or design of this study. WJF and SBG were involved in the acquisition of data. All authors were involved in the analysis and/or interpretation of the data, contributed to the development of the manuscript, and approved the final version for submission.

Conflicts of interests

WJF declares advisory board attendance and participation as a trial investigator for GSK, clinical trial funding from GSK, Sanofi, Mylan, ALK, Allergy Therapeutics, Novartis and Chordate, and personal fees from GSK and Sanofi; **JM** has received research grants from AstraZeneca, Genentech, GSK, Viatris, Novartis, Regeneron, Sanofi-Genzyme and Uriach Group, consulting fees from Sanofi-Genzyme and Uriach Group and attended speaker bureaus and/or advisory boards for AstraZeneca, Genentech, GSK, Glenmark, Menarini, Mitsubishi-Tanabe Pharma, MSD, Viatris, Novartis, Proctor & Gamble, Regeneron, Pharmaceuticals Inc., Sanofi Genzyme, UCB Pharma and Uriach Group; **DK** reports consultancy for Medtronic, Stryker, GSK, Entellus and NeurEnt**; CP** has participated in advisory boards for GSK, Sanofi and Stryker and has received institutional funding from the National Institute for Health Research**; VS** has participated in advisory boards for AstraZeneca, GlaxoSmithKline, Sanofi, and Novartis. **RCK** has received consultancy fees from Sanofi, GSK, Medtronicand he is the CMO of Lyra Therapeutics; **AC** has participated in advisory boards for GSK and Sanofi; **ARS**, **PHH**, **VSB**, **BM**, **SWY** and **RC** are employees of GSK and own stocks/shares; **SBG** declares consultancy and advisory board attendance for GSK, Sanofi Genzyme and UCB.

Tables

Table 1. Baseline demographics and clinical characteristics of patients with their last sinus surgery <3 and ≥3 years before screening

	Total N=407	Time since most recent sinus surgery prior to screening	
		<3 years n=180	≥3 years n=225
Duration of CRSwNP, years, mean (SD)	11.4 (8.4)	10.1 (9.2)	12.4 (7.6)
Previous sinus surgery[†], n (%)			
0	0	0	0
≥1	407 (100)	180 (100)	225 (100)
≥2	218 (54)	103 (57)	113 (50)
≥3	124 (31)	60 (33)	63 (28)
≥4	62 (15)	34 (19)	28 (12)
≥5	37 (9)	19 (11)	18 (8)
Time since previous sinus surgery[†], years, mean (SD) [range][‡]	4.0 (2.7) [0.03, 10.7]	1.6 (0.8) [0.03–3.00]	5.9 (2.1) [3.01–10.74]
SCS courses for CRSwNP in prior 12 months, n (%)			
0	210 (52)	93 (52)	116 (52)
≥1	197 (48)	87 (48)	109 (48)
≥2	86 (21)	41 (23)	45 (20)
Total endoscopic NPS, mean (SD) (scale: 0–8)	5.5 (1.3)	5.3 (1.3)	5.6 (1.2)
Nasal obstruction VAS score, mean (SD) (scale: 0–10)[§]	9.0 (0.8)	9.0 (0.8)	9.0 (0.8)
Overall VAS symptom score, mean (SD) (scale: 0–10)[§]	9.1 (0.7)	9.1 (0.7)	9.1 (0.8)
SNOT-22 score, mean (SD)[§] (scale: 0–110)	64.1 (18.3)	63.3 (18.5)	64.8 (18.2)
Patients with asthma, n (%)	289 (71)	132 (73)	155 (69)
Patients with N-ERD, n (%)	108 (27)	49 (27)	58 (26)
Blood eosinophil count, cells/µL, geometric mean (SD logs)	390 (0.8)	410 (0.8)	380 (0.7)

When reporting VAS outcomes in this study, patients quantified the severity of their symptoms on an electronic device that 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).

[†]Defined as any incision of the paranasal sinuses with resulting nasal polypectomy, in the last 10 years; [‡]includes patients with partial dates for previous surgery: if day was missing assumed as the last day of the month, if month was missing assumed as December; [§]higher scores indicate greater disease severity or worse quality of life.

CRSwNP, chronic rhinosinusitis with nasal polyps; N-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; SCS, systemic corticosteroids, SD, standard deviation; SNOT-22, Sino-nasal Outcome Test; VAS, visual analogue scale.

Table 2. Summary of sinus surgery endpoints (ITT population)

	Placebo (N=201)	Mepolizumab (N=206)
Need for sinus surgery up to Week 52		
Patients no longer needing sinus surgery at Week 52[†], n (%)[33]	103 (51)	149 (72)
Odds ratio, mepolizumab vs placebo (95% CI); p value[33]	2.46 (1.59, 3.79); p<0.001	
Patients included on a waiting list for sinus surgery prior to Week 52, n (%)	60 (30)	33 (16)
Hazard ratio, mepolizumab vs placebo (95% CI); p value	0.58 (0.38, 0.90); p=0.014	
Frequency, type and rate of sinus surgery up to Week 52		
Patients with 1 actual sinus surgery, n (%)	43 (21)	16 (8)
Patients with 2 actual sinus surgeries, n (%)	3 (1)	2 (<1)
Total number of sinus surgeries	49	20
FESS	35	11
Nasal polypectomy	14	9
Crude sinus surgery rate per patient per year[33]	0.25	0.10

[†]Defined as an overall symptom VAS score ≤7 (Weeks 49–52) and a total endoscopic NPS <5 (Week 52). When reporting VAS outcomes in this study, patients quantified the severity of their symptoms on an electronic device that 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).

CI, confidence interval; FESS, functional endoscopic sinus surgery; ITT, intent-to-treat; NPS, nasal polyp score.

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Figures Legends

Figure 1. Time to first inclusion on a waiting list for sinus surgery up to Week 52 (ITT population)

ITT, intent-to-treat; SC, subcutaneous.

Figure 2. Proportion of patients with a >1-point improvement from baseline in total endoscopic NPS and nasal obstruction VAS score, by the time since last sinus surgery before study screening

Time since last sinus surgery before screening was derived as: (date of screening - date of most recent NP surgery prior to screening + 1)/365.25. Partial dates were imputed as last day of the month and 'December' was used for dates with missing month. Date of sinus surgery was missing for one patient in the mepolizumab group and one patient in the placebo group. When reporting VAS outcomes in this study, patients quantified the severity of their symptoms on an electronic device that 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).
*Change from baseline to Week 52 (centrally read) in total endoscopic NPS and change from baseline to Weeks 49–52 in nasal obstruction VAS score; †time since last sinus surgery prior to study screening.
NPS, nasal polyp score; VAS, visual analogue scale.

Figure 3. Proportion of patients undergoing sinus surgery during the 52-week study period, by the time since last sinus surgery before screening

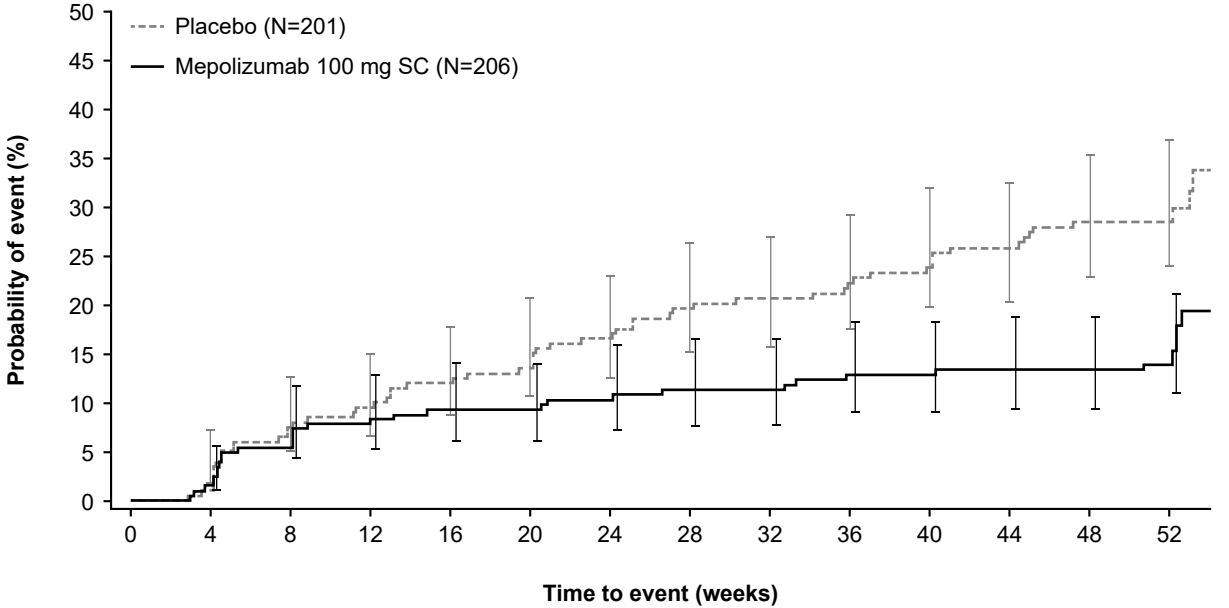
*Time since last sinus surgery prior to study screening.

Figure 4. Risk of sinus surgery during the study period, by the time since last surgery before study screening

Time since last sinus surgery before screening was derived as: (date of screening - date of most recent NP surgery prior to screening + 1)/365.25. Partial dates were imputed as last day of the month and 'December' was used for dates with missing month. Date of surgery was missing for one patient in the mepolizumab group and one patient in the placebo group.
CI, confidence interval.

Figure 5. Proportion of patients with 1, 2 or ≥3 sinus surgeries prior to study screening, by number of sinus surgeries reported during the study.

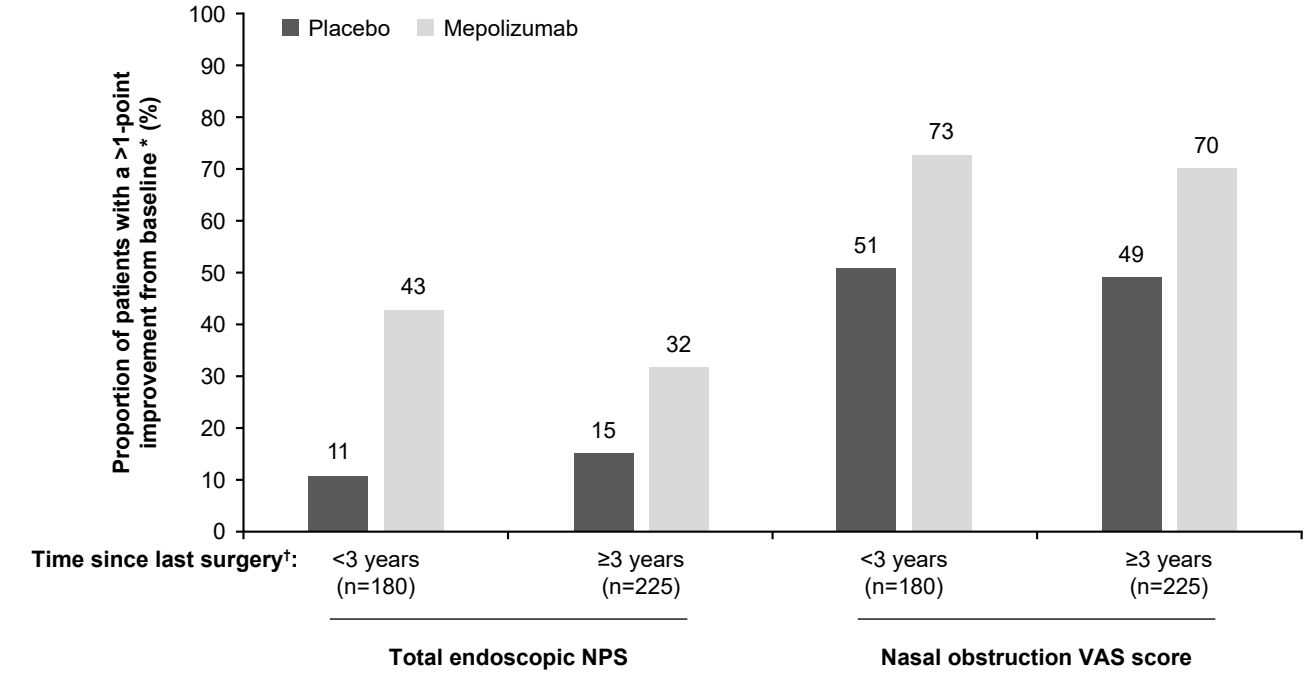
Figure 1. Time to first inclusion on a waiting list for sinus surgery up to Week 52 (ITT population)



No. at risk														
Placebo	201	199	185	181	175	171	164	156	154	150	146	141	135	105
Mepolizumab 100 mg SC	206	202	192	188	183	180	176	174	172	167	167	165	165	123

ITT, intent-to-treat; SC, subcutaneous.

Figure 2. Proportion of patients with a >1-point improvement from baseline in total endoscopic NPS and nasal obstruction VAS score, by the time since last sinus surgery before study screening



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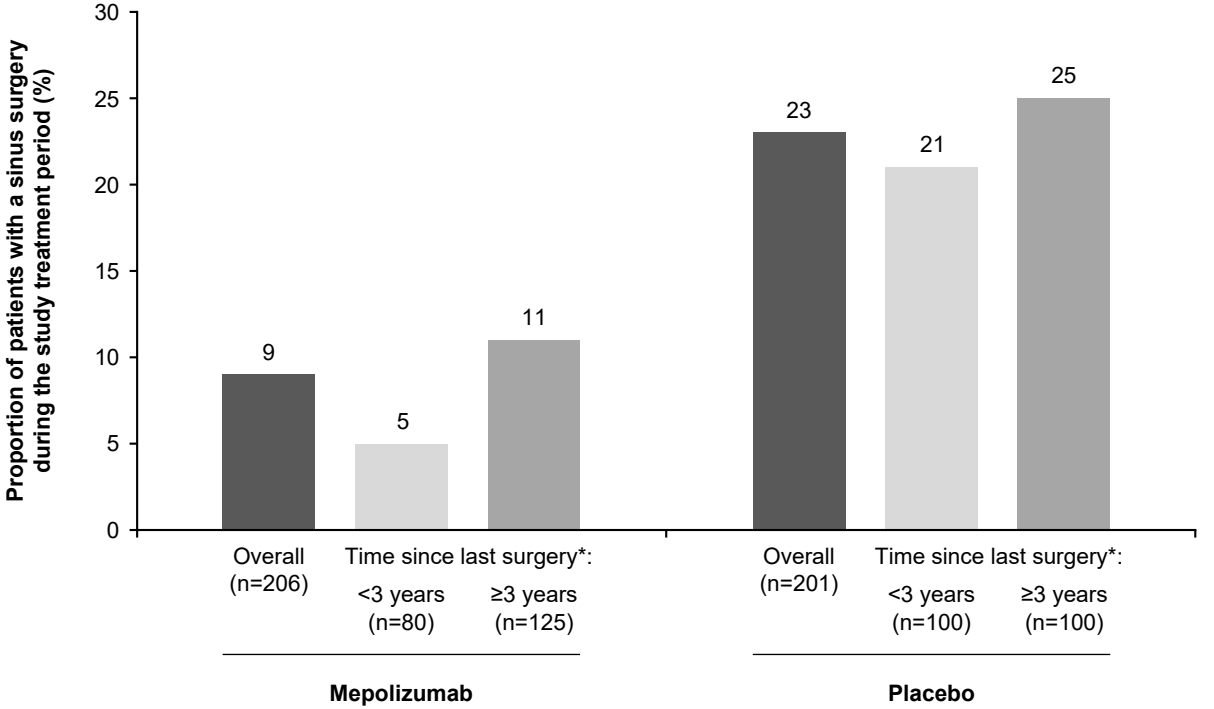
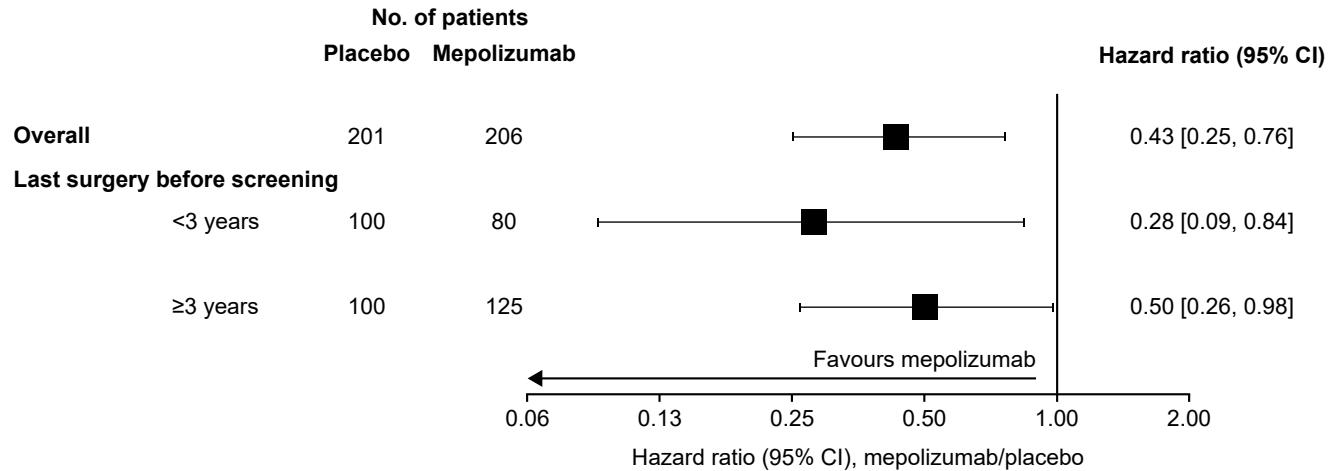


*Time since last sinus surgery prior to study screening.

Figure 4. Risk of sinus surgery during the study period, by the time since last surgery before study screening



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