Mepolizumab in CRSwNP/ECRS and NP: the phase III randomised MERIT trial in Japan, China, and Russia

Shigeharu Fujieda[1], Chengshuo Wang[2], Mamoru Yoshikawa[3], Mikiya Asako[4], Isao Suzaki[5], Claus Bachert[6], Joseph K. Han[7], Abby Fuller[8,9], Lee Baylis[10], Lin Su[11], Eri Sasaki[12], Ana R. Sousa[13], Robert Chan[13], Luo Zhang[2]

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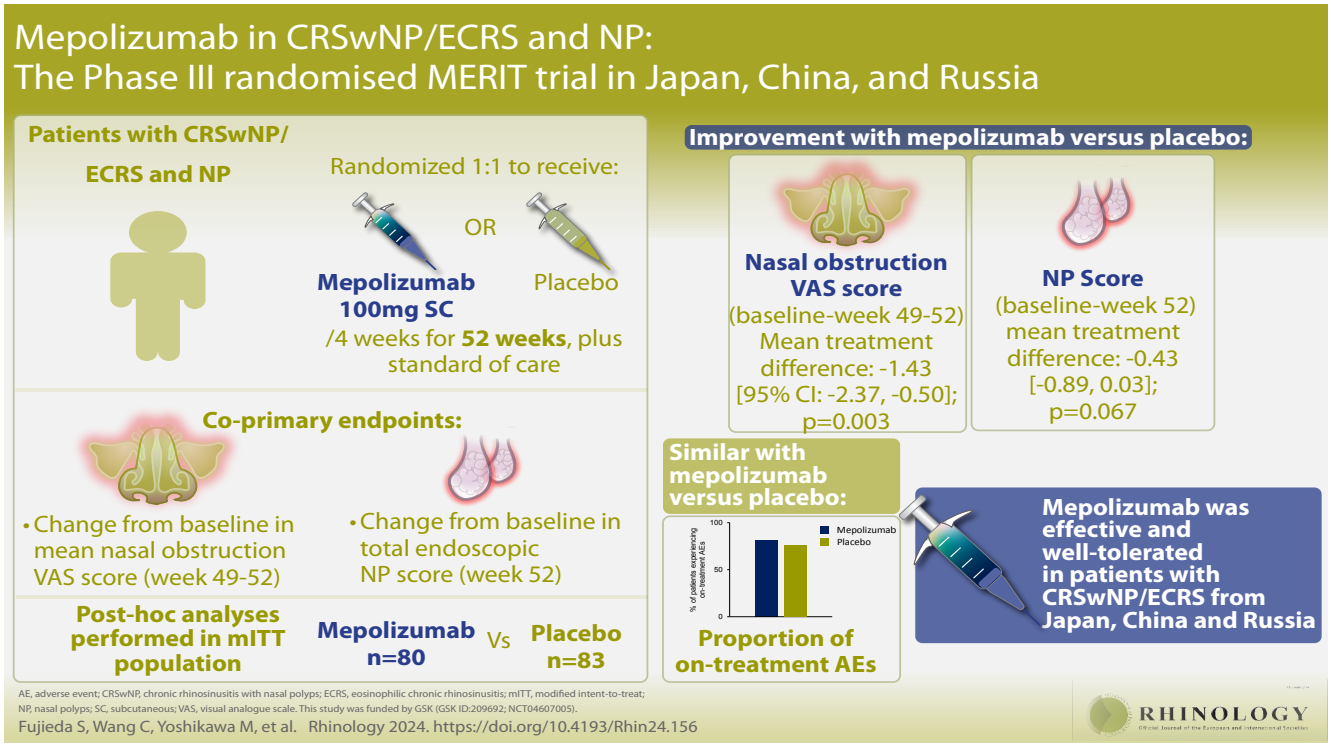

Abstract

Background: This randomised, double-blind, placebo-controlled, parallel-group, 52-week Phase III study (MERIT; NCT04607005) assessed mepolizumab efficacy and safety in patients with chronic rhinosinusitis with nasal polyps (CRSwNP)/eosinophilic CRS (ECRS) in Japan, Russia, and China, for which data are limited. **Methodology**: Eligible patients (enrolled at 60 centres) had blood eosinophil count >2%, endoscopic bilateral NP score ≥5, nasal obstruction visual analogue scale (VAS) score >5, ≥2 sinonasal symptoms, and either previous sinus surgery or systemic corticosteroid use/intolerance. Patients were randomised (1:1) to receive mepolizumab 100 mg subcutaneously or placebo every 4 weeks, plus standard of care. Co-primary endpoints: change from baseline in total endoscopic NP score (ENPS) (Week 52) and nasal obstruction VAS score (Weeks 49–52). Post hoc analyses conducted in a modified intent-to-treat (mITT) population excluded patients from two study sites, related to Good Clinical Practice violations by the Site Management Organisation overseeing these sites. These were considered the primary efficacy analyses. **Results**: In the mITT population, mepolizumab (n=80) versus placebo (n=83) significantly improved nasal obstruction VAS score from baseline to Week 49–52 and was associated with a trend of total ENPS improvements at Week 52. Mepolizumab/placebo on-treatment adverse events (AEs) occurred in 68/84 and 65/85 patients in the safety population (treatment-related AEs: 2/84 and 5/85, respectively), and on-treatment serious AEs in 0/84 and 4/85 patients, respectively (no fatalities reported). **Conclusions**: Mepolizumab was effective and well-tolerated in patients with CRSwNP/ECRS from Japan, Russia, and China.

Key words: eosinophils, interleukin-5, mepolizumab, nasal polyps, rhinosinusitis

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is present in 1.0–2.6% of the population, and is characterised by chronic, recurrent nasal and paranasal inflammation and secondary growths of sinonasal tissue into nasal polyps (NP) [1, 2]. CRSwNP is frequently associated with asthma [3], with interleukin (IL)-5 being a dominant cytokine driving Type 2 pathological inflammation in CRSwNP [4]. Common sinonasal symptoms include nasal obstruction, loss of sense of smell, nasal discharge, facial pain and pressure, and sleep disturbances [5], which have substantial burden on quality of life (QoL) [6]. In East Asia, CRSwNP has previously been more associated with neutrophilic inflammation and, consequently, is differentiated into types by the presence of eosinophils or neutrophils, with the former referred to as eosinophilic chronic rhinosinusitis (ECRS) [7, 8]. In Japan, the presence of ECRS is confirmed using the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) scoring system [9]. Most patients with ECRS per JESREC scoring have NP, and this forms a component of the scoring system (9). Eosinophilic inflammation is associated with CRSwNP severity, refractory responses to treatment, and frequency of disease recurrence [10, 11]. In particular, eosinophil extracellular trap formation (ETosis) leads to the formation of Charcot–Leyden crystals (CLC), which contribute to chronic inflammation and tissue damage due to the properties of highly viscous eosinophilic mucin and impairments in mucin clearance [12-15]. Additionally, ETosis and CLC concentrations are associated with disease severity, while CLC concentrations are associated with olfactory dysfunction and are predictive of the risk of CRSwNP recurrence [10, 16-18]. Recurrences of NP are common due to the lack of an effective durable therapy [6, 19] and, consequently, patients with CRSwNP/ECRS and NP have a high burden of disease, further exacerbated by a high prevalence of comorbidities such as aspirin-exacerbated respiratory disease (AERD) [19].

Biologic therapies targeting eosinophilic and Type 2 inflammation are now available as add-on options to existing standard of care (SoC) treatment, including intranasal corticosteroids (INCS) and systemic corticosteroids (SCS) for severe CRSwNP, and for patients with disease refractory to these treatments, sinus surgery [5, 20, 21]. This includes mepolizumab, a first-in-class humanised monoclonal antibody that specifically targets IL-5, the primary cytokine responsible for the proliferation, activation, and survival of eosinophils [22]. Mepolizumab is approved as an add-on treatment in adults for CRSwNP in multiple countries based on results of the Phase III SYNAPSE trial, conducted in 11 countries worldwide [23-25]. Results from SYNAPSE showed that mepolizumab treatment reduced NP size, nasal obstruction, and sinonasal symptoms, improved sinonasal disease-specific QoL, and increased time to sinus surgery versus placebo (24). However, the SYNAPSE trial did not include patients from China or Japan, and mepolizumab is not currently approved for use in patients with CRSwNP in China or Japan. There are differences in disease profiles between populations in Asia and Europe [26]; however, to date, there are limited data on mepolizumab efficacy and safety in patients with CRSwNP in these countries [27]. Consequently, there remains an unmet need for novel treatment to reduce the burden of disease for patients with CRSwNP/ECRS and NP in China and Japan, including reducing the need for sinus surgery [28, 29].

The objective of the Phase III MERIT study was to assess the efficacy and safety of mepolizumab in patients with CRSwNP/ECRS and NP in China, Japan and Russia.

Materials and methods

Study design

MERIT was a Phase III, randomised, double-blind, placebo-controlled, parallel-group study (GSK ID: 209692; NCT04607005) conducted at 60 study centres in three countries (Japan [37], Russia [7], and China [16]). After a 4-week run-in period, patients were randomised (1:1) to receive mepolizumab 100 mg subcutaneous or placebo every 4 weeks, in addition to SoC, for 52 weeks (Supplementary Figure 1).

Randomisation and masking

The randomisation sequence was generated by the GSK-validated randomisation software RandALL NG (version 1.1.3) and performed separately for each country and stratified by background INCS use, using a permuted block design of block size four. Investigators were informed of patients' treatment assignment via an interactive response technology system. Site staff, the central study team, and patients were masked to both study treatment by use of identical appearance mepolizumab and placebo and absolute blood eosinophil counts (including white blood cell differentials) for the duration of the trial.

The trial was done in accordance with 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.

Patients

Eligible patients had a diagnosis of bilateral CRSwNP/ECRS consistent with the JESREC algorithm [9], a blood eosinophil count >2% in the 12 months prior to screening, an endoscopic bilateral NP score ≥5 (minimum score of 2 in each nasal cavity), and a nasal obstruction visual analogue scale (VAS) symptom score >5 for the 12 weeks prior to screening. At randomisation, patients required a JESREC score ≥11 [9] and a mean nasal obstruction VAS score >5 in the 7 days preceding randomisation. Additionally, patients were required to have ≥1 of nasal blockage/obstruc-

tion/congestion or nasal discharge (anterior/posterior nasal drip) and ≥1 of facial pain/pressure and/or reduction of loss of smell. Patients were also required to meet at least one of the following three criteria: 1) previous sinus surgery for the removal of NP (surgery within the previous 6 months prior to treatment was excluded), 2) ≥3 consecutive days of SCS in the previous 2 years (for the treatment of NP), or 3) medically unsuitable for or intolerant to SCS. Patients were not required to be using INCS (including inhaled corticosteroids and etanercept), but dose changes in INCS, intranasal inhaled corticosteroids (ICS), and leukotriene receptor antagonist (LTRA) therapy were not permitted within 30 days of screening.

Excluded patients included those with herpes zoster within 3 months of screening; evidence of tuberculosis, cystic fibrosis, eosinophilic granulomatosis with polyangiitis; Young's, Kartagener's, or dyskinetic ciliary syndromes; antrochoanal polyps, severe nasal septal deviation preventing full assessment of NP, acute sinusitis or an upper respiratory tract infection (within 2 weeks of screening), ongoing rhinitis medicamentosa, human immunodeficiency virus infection, or parasitic infestation within 6 months prior to screening. Patients who had received chemotherapy, radiotherapy, or mepolizumab (within 3 months of study, or 5 half-lives), and those with a history of allergic reaction to anti-IL-5 or other monoclonal antibody therapy, who had an asthma exacerbation requiring hospital admission within 4 weeks of screening, who had undergone sinus surgery within 6 months prior to screening, and for whom sinus surgery was contraindicated were also excluded.

Patients who had undergone or were on a waiting list for sinus surgery, had significant laboratory abnormalities, or had dose changes in INCS, intranasal ICS, LTRA, oral corticosteroid (OCS), or allergen immunotherapy were excluded.

Procedures

In addition to randomised treatment, patients received SoC treatments in accordance with local practice, which could have included optional daily INCS and saline nasal douching, occasional short courses of high-dose OCS, and/or antibiotics when required.

Endoscopic NP score (ENPS) (range: 0–4 for each nostril, with higher scores representing greater obstruction) was assessed by trained healthcare staff at each study visit, with endoscopic images centrally scored by independent masked reviewers. A daily eDiary was used during run-in and the treatment period to record symptoms (nasal obstruction, nasal discharge, throat mucus, loss of smell, facial pain, and overall symptoms) using a VAS scale (0–100, with higher scores indicating worse status); scores were divided by 10 and reported across a range from 0.0 (none) to 10.0 (as bad as you can imagine). Lund–Mackay (LMK) computerised tomography (CT) was performed during the run-in period and Week 52/early withdrawal visit. Scoring was based on localisation, with points given for degree of opacification (0–2, with higher scores indicating more opacification), applied to the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, or frontal sinus on each side. The 22-item Sino-Nasal Outcome Test (SNOT-22) was completed by patients at each 4-weekly study visit. SNOT-22 scores ranged from 0 to 110, with a minimal clinically important difference of 8.9 units [30].

Outcomes

The co-primary endpoints were change from baseline in centrally read total ENPS at Week 52 and mean nasal obstruction VAS score during Weeks 49–52.

Secondary endpoints were change from baseline in mean overall VAS score during Weeks 49–52, LMK-CT score at Week 52, mean composite VAS score during Weeks 49–52 (nasal obstruction, nasal discharge, mucus in the throat, and loss of smell), SNOT-22 total score at Week 52 and mean loss of smell VAS score during Weeks 49–52, and time to first sinus surgery or course of SCS for CRSwNP/ECRS. Other endpoints included the proportion of patients with a ≥1-point improvement in total ENPS and nasal obstruction VAS at Week 52 and the effect of background INCS use on the co-primary endpoints.

Safety assessments included monitoring of adverse events (AEs), serious AEs (SAEs), and AEs of special interest (allergic reactions, local site reactions, infections including opportunistic infections; neoplasms, malignancies, and cardiac disorders). AEs and SAEs were coded per the Medical Dictionary for Regulatory Activities (26.0).

Sample size and statistical analysis

The sample size for the intent-to-treat (ITT) population was based on the co-primary efficacy endpoints of total ENPS at Week 52 and nasal obstruction VAS score during the 4 weeks prior to Week 52. The sample size of 160 patients randomised in a 1:1 ratio to each treatment arm was estimated to provide ≥90% power to detect a statistical significance (at two-sided significance of 0.05) for co-primary endpoints using a mixed-model repeated measures analysis model. Observed differences between treatments of ≥0.57 units for total ENPS and ≥1.01 for nasal obstruction VAS score would achieve statistical significance assuming standard deviations of 1.82 and 3.25, respectively.

Efficacy endpoints were initially assessed in the ITT population, defined as all randomised patients who received ≥1 dose of the study drug, analysed according to the allocated treatment (see below for details of post hoc analyses in the modified ITT [mITT] population). Safety was assessed in the safety population, defined as all randomised patients who received ≥1 dose of the study drug, analysed according to the treatment received for >50% of administrations.

To control for multiplicity of statistical testing, hypotheses associated with the two primary and six secondary endpoints were

tested using a gatekeeping procedure based on a graphical approach to sequentially rejective multiple test procedures [31]. The hierarchy used is illustrated in Supplementary Figure 2. The hierarchy of secondary endpoints was: change from baseline in mean overall VAS score during Weeks 49–52, LMK-CT score at Week 52, mean composite VAS score during Weeks 49–52, SNOT-22 total score at Week 52 and mean loss of smell VAS score during Weeks 49–52, and time to first sinus surgery or course of SCS for CRSwNP/ECRS.

Patients who had sinus surgery before Week 52 were assigned the worst possible score across all participants for all subsequent visits. In the primary analysis, a treatment policy approach was applied for premature discontinuation of study treatment unrelated to COVID-19, changes in background medication or start of a prohibited medication unrelated to COVID-19, or a course of SCS for CRSwNP/ECRS. Premature discontinuation of study treatment, change in background medication, or the start of prohibited medication related to COVID-19 was handled using a hypothetical strategy. For the co-primary endpoints, a sensitivity analysis was performed for patients who underwent sinus surgery or a course of SCS up to Week 52, with the worst possible score assigned for all visits following the event.

For the co-primary endpoints, VAS scores, LMK-CT, and SNOT-22 total score, the differences in change from baseline scores between treatment groups were assessed using the mixed-model repeated model, adjusting for covariates of baseline value, log baseline blood eosinophil count, background INCS use, country, and timepoint, presented as a difference in means between treatment groups. Time to sinus surgery or first course of SCS use was analysed using a Cox proportional hazards model with covariates of treatment, log baseline blood eosinophil count, number of previous surgeries, background INCS use, and country. The proportion of responders for the co-primary endpoints was analysed using logistic regression, with covariates of treatment, baseline score, log baseline blood eosinophil count, background INCS use, and country.

Post hoc analyses

After study completion, the study sponsor was informed by the Japan Ministry of Health, Labour and Welfare of Good Clinical Practice (GCP) violations in several clinical studies by a site management organisation (SMO) that managed two Japanese sites that participated in MERIT. No evidence of data falsification relating to MERIT was observed during a sponsor audit at these sites, and the objective measures in this study were verified independently. Nonetheless, post hoc analyses were conducted in a mITT for the co-primary, secondary efficacy, and responder endpoints excluding all patients from the two study sites (252027 and 252048). These were considered the primary efficacy analyses.

Results

Patient population

Patients were recruited from 8 February 2021 to 24 March 2022 and follow-up continued until 12 April 2023. Of the 327 patients screened, 169 underwent randomisation and were included in the ITT population. In total, 84 patients received mepolizumab and 85 patients received placebo (Supplementary Figure 3). In total, 22 patients (mepolizumab, n=6; placebo, n=16) discontinued treatment, and after varying durations of off-treatment assessments, all 22 patients were withdrawn prior to Week 52. The most common primary reasons for withdrawal were withdrawal by patient (mepolizumab, n=4; placebo, n=9) and lack of efficacy (mepolizumab, n=1; placebo, n=6). In the mITT population, six patients were excluded based on study site (mepolizumab, n=4; placebo, n=2).

Patient baseline demographics and clinical characteristics were generally similar between treatment groups and were consistent between the mITT and ITT populations (Table 1). In the mITT population, a total of 91 (52%) of patients were Japanese, 48 (29%) were Russian, and 30 (18%) were Chinese.

Co-primary endpoints

Least squares (LS) mean change (standard error [SE]) from baseline in nasal obstruction VAS score at Weeks 49–52 was significantly greater with mepolizumab (-3.2 [0.34]) versus placebo (-1.8 [0.33]) (mean treatment difference: -1.43 [95% confidence interval {CI}: -2.37, -0.50]; p=0.003) in the mITT population (Figure 1A). A very similar result was seen in the ITT population (mean treatment difference: -1.43 [95% CI: -2.35, -0.51]; p=0.002) (Figure 1B). LS mean change (SE) from baseline in total ENPS at Week 52 was numerically greater for patients receiving mepolizumab (-0.62 [0.16]) versus placebo (-0.19 [0.164]) equating to a mean treatment difference -0.43 [95% CI: -0.89, 0.03]; p=0.067) (Figure 2A). Whereas in the ITT population the mean treatment difference was slightly larger and achieved statistical significance (-0.47 [95% CI: -0.92, -0.02; p=0.043]) (Figure 2B). These trends were maintained irrespective of baseline blood eosinophil counts (Supplementary Table 1).

Secondary endpoints

At Weeks 49–52, improvements from baseline in mean overall VAS score were significantly greater with mepolizumab versus placebo (difference: -1.54 [-2.52, -0.55]; p=0.003) in the mITT population. Similarly, mepolizumab versus placebo treatment resulted in significantly greater improvements from baseline in LMK-CT score at Week 52 (difference: -1.63 [-2.90, -0.37]; p=0.012), mean composite VAS score for nasal symptoms at Weeks 49–52 (difference: -1.17 [-1.99, -0.35]; p=0.005), SNOT-22 total score at Week 52 (difference: -10.63 [-18.68, -2.57]; p=0.01 [adjusted]), and loss of smell VAS score at Weeks 49–52 (difference: -0.82 [-1.43, -0.21]; p=0.009). Similar trends were observed

Table 1. Baseline demographics and clinical characteristics.

	mITT		ITT	
	Mepolizumab 100 mg SC (N=80)	**Placebo (N=83)**	**Mepolizumab 100 mg SC (N=84)**	**Placebo (N=85)**
Age, years, mean (SD)	53 (10.7)	52 (13.2)	52 (10.5)	52 (13.2)
Female, n (%)	29 (36)	29 (35)	31 (37)	29 (34)
BMI, kg/m², mean (SD)	25.5 (3.15)	24.6 (4.24)	25.5 (3.12)	24.7 (4.21)
Race, n (%)				
Asian	56 (70)	59 (71)	60 (71)	61 (72)
White	24 (30)	24 (29)	24 (29)	24 (28)
Country, n (%)				
Japan	41 (51)	44 (53)	45 (54)	46 (54)
Russia	24 (30)	24 (29)	24 (29)	24 (28)
China	15 (19)	15 (18)	15 (18)	15 (18)
Smoking history, n (%)				
Never smoked	44 (55)	61 (73)	45 (54)	62 (73)
Current smoker	14 (18)	6 (7)	16 (19)	7 (8)
Former smoker	22 (28)	16 (19)	23 (27)	16 (19)
Duration of NP, years, mean (SD)	n=77 12.0 (9.19)	n=81 11.0 (9.11)	n=81 11.9 (9.09)	n=83 10.9 (9.08)
Number of previous surgeries, n (%)			n=84	n=84*
0	28 (35)	29 (35)	29 (35)	31 (37)
≥1	52 (65)	53 (64)	55 (65)	53 (64)
≥2	25 (31)	23 (28)	25 (29)	23 (28)
≥3	14 (18)	9 (11)	14 (16)	9 (11)
≥4	7 (9)	7 (8)	7 (8)	7 (9)
≥5	4 (5)	3 (4)	4 (5)	3 (4)
Maintenance INCS use at baseline, n (%)	58 (73)	64 (77)	61 (73)	64 (75)
Baseline blood eosinophil count, cells/μL, geo. mean (log SD)	400 (0.641)	460 (0.700)	390 (0.629)	450 (0.700)
Courses of SCS in last 12 months,† n (%)				
0	41 (52)	35 (42)	42 (50)	35 (41)
≥1	39 (49)	48 (58)	42 (51)	50 (59)
≥2	12 (15)	10 (12)	12 (15)	10 (12)
≥3	7 (9)	4 (5)	7 (9)	4 (5)
≥4	4 (5)	3 (4)	4 (5)	3 (4)
≥5	3 (4)	3 (4)	3 (4)	3 (4)
Total ENPS (scale 0–8),‡§ mean (SD)	5.9 (1.27)	6.1 (1.25)	5.9 (1.26)	6.1 (1.26)
Nasal obstruction VAS score (scale 0–10),¶ mean (SD)	8.60 (1.25)	8.59 (1.26)	8.62 (1.24)	8.61 (1.26)
Overall VAS score (scale 0–10), mean (SD)	8.65 (1.58)	8.52 (1.55)	8.68 (1.55)	8.54 (1.54)
LMK CT score (scale 0–24), mean (SD)	20.3 (3.25)	20.7 (3.44)	20.2 (3.30)	20.5 (3.55)
Composite VAS score (nasal symptoms)‖ (scale 0–10), mean (SD)	8.22 (1.34)	8.38 (1.19)	8.25 (1.34)	8.39 (1.18)
Baseline SNOT-22 total score (scale 0–110), mean (SD)	56.9 (18.94)	55.6 (20.22)	57.2 (18.82)	56.4 (20.61)
Loss of smell VAS score (scale 0–10), mean (SD)	9.37 (1.21)	9.48 (1.00)	9.33 (1.26)	9.48 (1.00)
JESREC score# (scale 0–17), mean (SD)**	14.0 (2.61)	14.4 (2.48)	13.9 (2.59)	14.3 (2.50)

	mITT		ITT	
	Mepolizumab 100 mg SC (N=80)	Placebo (N=83)	Mepolizumab 100 mg SC (N=84)	Placebo (N=85)
JESREC score[#] (scale 0–17), n (%)**				
<11	3 (4)	2 (2)	3 (4)	2 (2)
≥11–<13	23 (29)	20 (24)	25 (30)	22 (26)
≥13–<15	37 (46)	39 (47)	39 (46)	39 (46)
≥15–17	17 (21)	22 (27)	17 (20)	22 (26)
Concurrent asthma, n (%)	64 (80)	67 (81)	66 (79)	67 (79)
Aspirin or other NSAID intolerance, n (%)	23 (29)	38 (46)	25 (30)	38 (45)

*For 1 patient, the number of previous surgeries is unknown; [†]For NP; [‡]20 patients with baseline total NP score <5, 4 China, 12 Japan, 4 Russia; [§]At screening, mean (SD) total ENPS was 6.1 (0.94)/6.3 (1.09) in the mITT and 6.0 (0.94)/6.4 (1.09) in the ITT population; [¶]In the 7 days prior to randomisation; [‖]Includes nasal obstruction, nasal discharge, mucus in the throat, and loss of smell; [#]A score ≥11 confirms a diagnosis of ECRS; **Patient enrolment based on JESREC scores at screening, required to be ≥11. (m)ITT, (modified) intent-to-treat; BMI, body mass index; CT, computerised topography; ECRS, eosinophilic chronic rhinosinusitis; ENPS, endoscopic nasal polyp score; INCS, intranasal corticosteroid; ITT, intent-to-treat; JESREC, Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis; LMK, Lund–Mackay; NP, nasal polyps; NSAID, non-steroidal anti-inflammatory drug; SC, subcutaneous; SCS, systemic corticosteroid; SD, standard deviation; SNOT-22, Sino-Nasal Outcome Test, 22 questions; VAS, visual analogue scale.

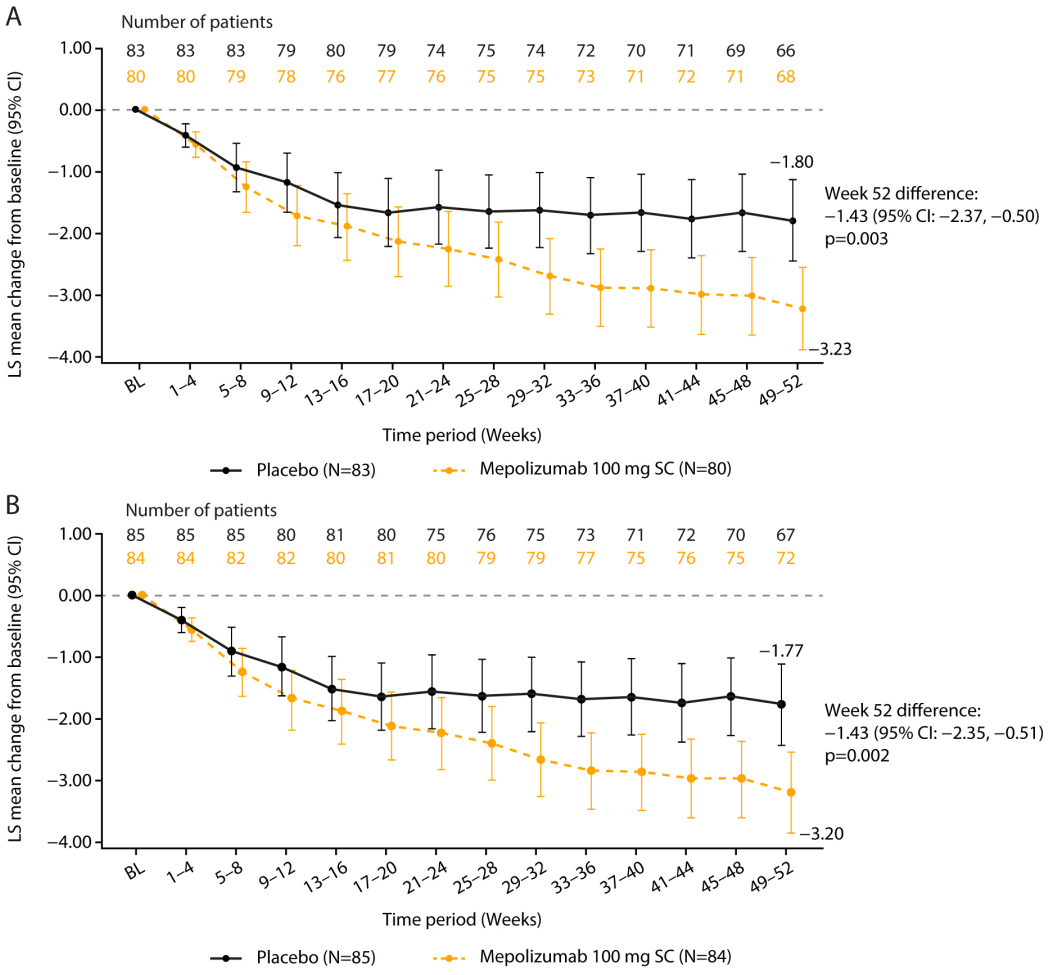

Figure 1. LS mean change from baseline in mean nasal obstruction VAS score by 4-week period in the (A) mITT and (B) ITT population. Error bars represent 95% CI; patients who had sinus surgery before Week 52 were assigned the worst possible score for all post-surgery assessments. (m)ITT, (modified) intent-to-treat; BL, baseline; CI, confidence interval; LS, least squares; SC, subcutaneous; VAS, visual analogue scale.

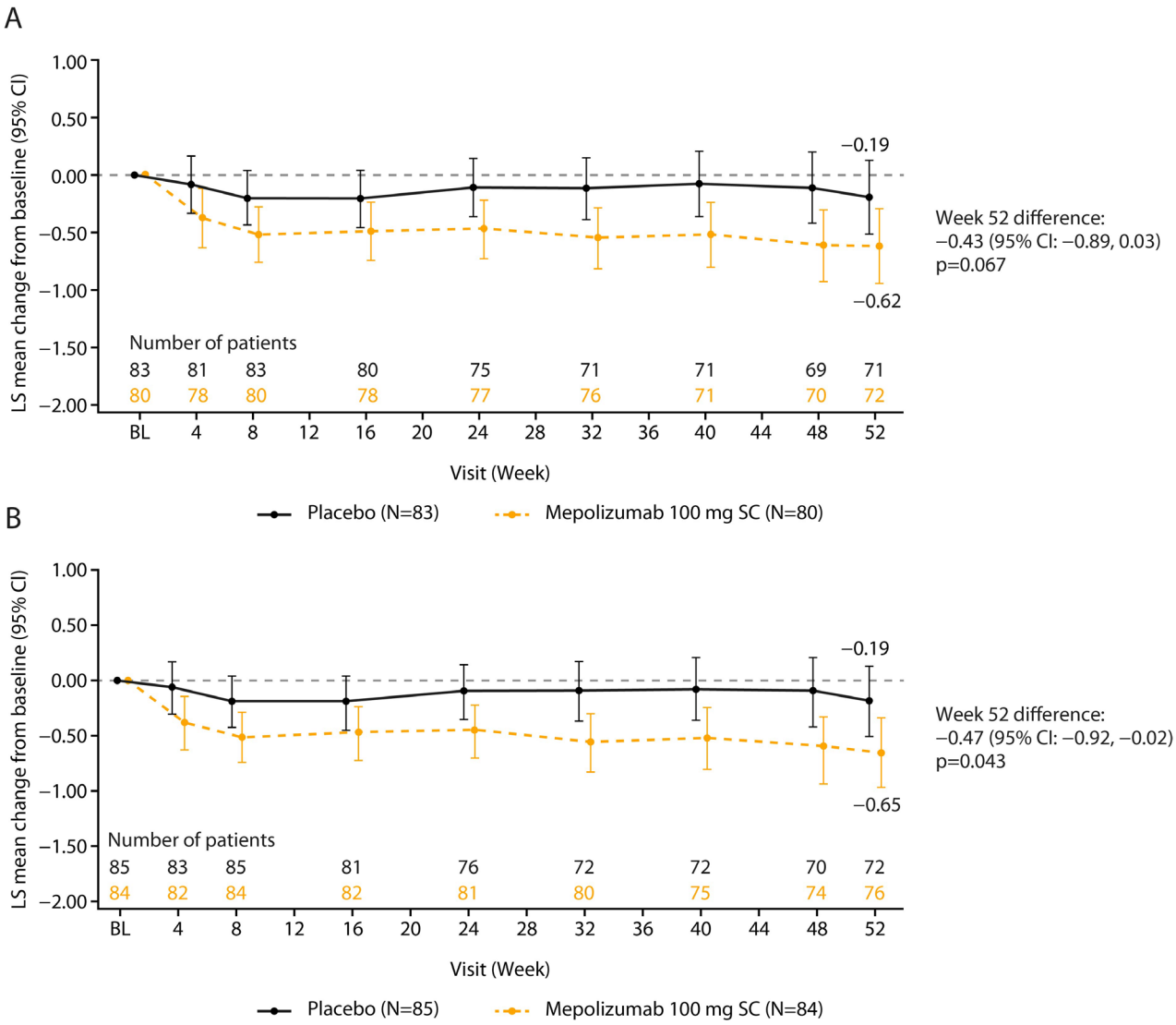

Figure 2. LS mean change from baseline in total ENPS by 4-week period in the (A) mITT and (B) ITT population. Error bars represent 95% CI; patients who had sinus surgery before Week 52 were assigned the worst possible score for all post-surgery assessments. (m)ITT, (modified) intent-to-treat; BL, baseline; CI, confidence interval; ENPS, endoscopic nasal polyp score; LS, least squares; SC, subcutaneous.

in the ITT population (Table 2).

Patients receiving mepolizumab also had a reduced risk of sinus surgery or course of SCS for CRSwNP/ECRS compared with patients receiving placebo (hazard ratio: 0.49 [95% CI: 0.26, 0.92]; p=0.026) (Figure 3A). This was consistent with results in the ITT population (Figure 3B).

Other endpoints and sensitivity analysis

The odds of a patient being defined as a responder based on total ENPS were higher at all weeks for patients treated with mepolizumab compared with placebo in both the mITT and ITT populations (Supplementary Figure 4A and B), with this benefit seen from Week 4 onwards (mITT Week 4 odds ratio [OR] [95% CI]: 2.43 [1.19, 4.95]; p=0.015). Similarly, the odds of a patient being defined as a responder for mean nasal obstruction VAS score were higher for the mepolizumab group compared with placebo across the duration of the study in both ITT and mITT populations and became statistically significant from Weeks 29–32 onwards (mITT Weeks 29–32 OR [95% CI]: 2.61 [1.29, 5.28]; p=0.008), and this was maintained for the remainder of the study (Supplementary Figure 5A and B).

Treatment differences in change from baseline in total ENPS and VAS nasal obstruction score were numerically greater in patients with background INCS use versus no use (Supplementary Figure 6A and B) and in patients with a history of more surgeries (Supplementary Figure 7A and B).

Numerical improvements in both co-primary endpoints with mepolizumab versus placebo were still observed when using worst possible scores for nasal obstruction VAS and total endoscopic NP after first course of SCS (in the primary analyses, only

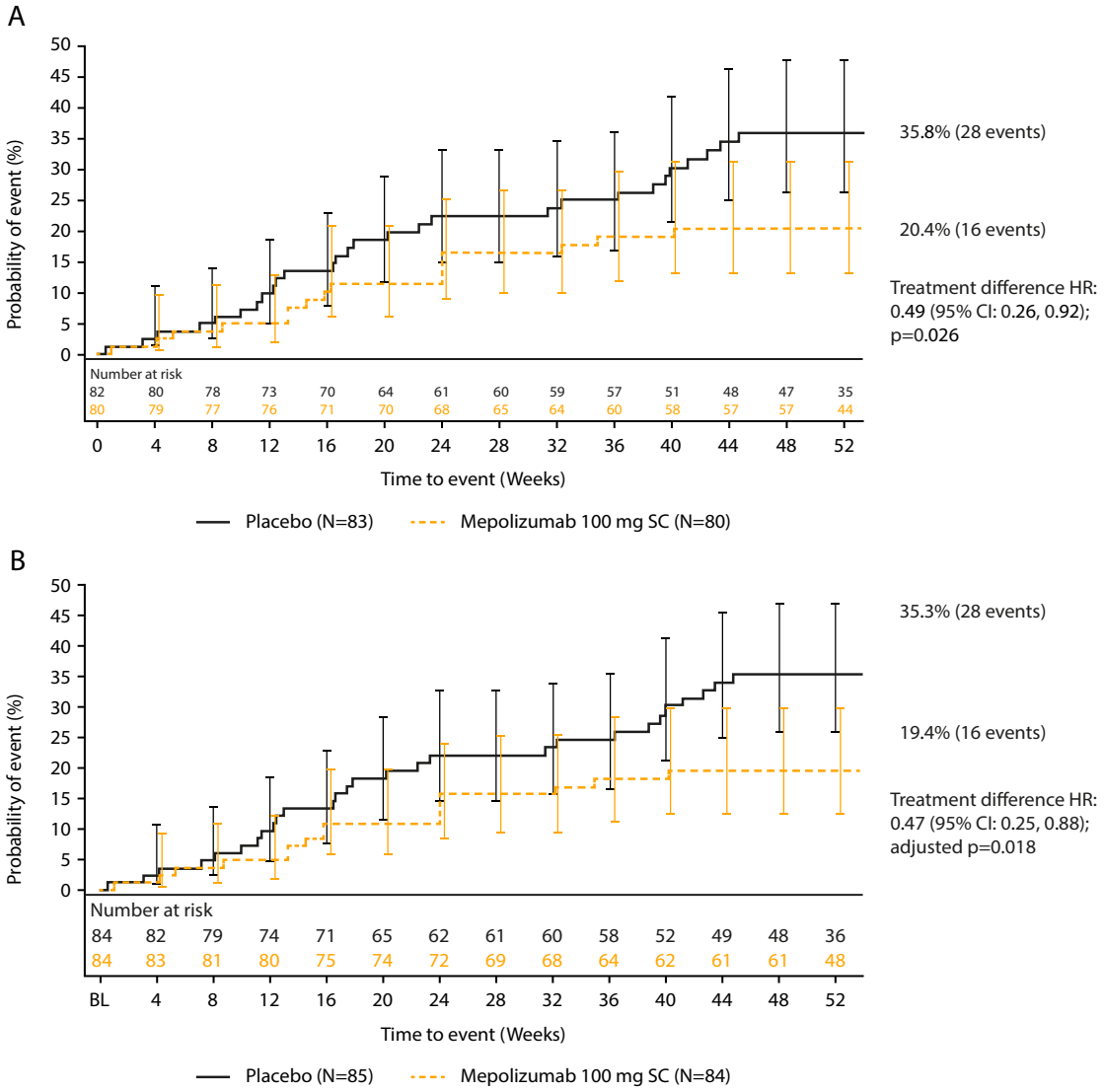

Figure 3. Time to sinus surgery or course of SCS for patients with CRSwNP/ECRS in the (A) mITT and (B) ITT population. (m)ITT, (modified) intent-to-treat; BL, baseline; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; ECRS, eosinophilic chronic rhinosinusitis; HR, hazard ratio; SC, subcutaneous; SCS, systemic corticosteroid.

patients with nasal surgery were assigned the worst possible score for all visits after surgery) (Supplementary Figure 8). Treatment differences and hazard ratios for the primary and secondary endpoints in the mITT and ITT populations are summarised together in Figure 4.

Safety

A similar proportion of patients experienced on-treatment AEs in the mepolizumab (68/84 [81%]) and placebo (65/85 [76%]) groups (Supplementary Table 2). In total, seven patients had treatment-related AEs (five in the placebo group and two in the mepolizumab group); none of these were SAEs. The two patients in the mepolizumab group with treatment-related AEs had a liver event (increased alanine transaminase and aspartate aminotransferase levels), which resolved, and multiple events (headache, bone and facial pain, and oropharyngeal pain with dysphonia), respectively. There were two patients in the placebo group who had an AE leading to permanent discontinuation of study treatment and withdrawal: one for drug-induced liver injury and one for breast cancer.

In both the mepolizumab and placebo groups, the most common AEs were COVID-19 (18% and 18%), nasopharyngitis (11% and 8%), and headache (7% and 7%) (Supplementary Table 2). In total, four patients experienced SAEs (asthma, CRSwNP, bullous pemphigoid, and breast cancer), all in the placebo group. There were no fatal AEs. A similar proportion of patients experienced AEs of special interest.

Table 2. Summary of secondary endpoint efficacy outcomes (ITT population).

	mITT		ITT	
	Mepolizumab 100 mg SC (N=80)	Placebo (N=83)	Mepolizumab 100 mg SC (N=84)	Placebo (N=85)
Change from baseline in mean overall VAS score at Weeks 49–52*				
LS mean (SE)	5.26 (0.354)	6.79 (0.352)	5.30 (0.346)	6.84 (0.350)
LS mean change (SE)	-3.33 (0.354)	-1.80 (0.352)	-3.31 (0.346)	-1.77 (0.350)
Difference (95% CI); p-value	-1.54 (-2.52, -0.55); p=0.003†		-1.54 (-2.51, -0.57); adjusted p=0.023‡	
Change from baseline in LMK-CT score at Week 52				
LS mean (SE)	16.89 (0.449)	18.52 (0.452)	16.77 (0.442)	18.44 (0.454)
LS mean change (SE)	-3.52 (0.449)	-1.88 (0.452)	-3.55 (0.442)	-1.88 (0.454)
Difference (95% CI); p-value	-1.63 (-2.90, -0.37); p=0.012†		-1.67 (-2.93, -0.42); adjusted p=0.023‡	
Change from baseline in mean composite VAS score (nasal symptoms)§ at Weeks 49–52*				
LS mean (SE)	5.66 (0.294)	6.83 (0.291)	5.68 (0.289)	6.89 (0.291)
LS mean change (SE)	-2.64 (0.294)	-1.47 (0.291)	-2.64 (0.289)	-1.44 (0.291)
Difference (95% CI); p-value	-1.17 (-1.99, -0.35); p=0.005†		-1.21 (-2.02, -0.40); adjusted p=0.023‡	
Change from baseline in total SNOT-22 score at Week 52¶				
LS mean (SE)	37.99 (2.889)	48.62 (2.869)	37.82 (2.771)	49.21 (2.806)
LS mean change (SE)	-18.27 (2.889)	-7.65 (2.869)	-18.98 (2.771)	-7.58 (2.806)
Difference (95% CI); p-value	-10.63 (-18.68, -2.57); p=0.01†		-11.39 (-19.19, -3.60); adjusted p=0.023‡	
Change from baseline in loss of smell VAS score at Weeks 49–52*				
LS mean (SE)	7.71 (0.220)	8.53 (0.219)	7.64 (0.215)	8.53 (0.219)
LS mean change (SE)	-1.71 (0.220)	-0.89 (0.219)	-1.76 (0.215)	-0.87 (0.219)
Difference (95% CI); p-value	-0.82 (-1.43, -0.21); p=0.009†		-0.89 (-1.49, -0.28); adjusted p=0.023‡	

*Patients who had sinus surgery before Week 52 were assigned the worst possible score for all post-surgery assessments; †Unadjusted p values; ‡Adjusted p values for secondary endpoints, multiplicity controlled using a closed testing procedure according to a predefined hierarchy of testing; §Including nasal obstruction, nasal discharge, throat mucus, and loss of smell; ¶One patient (mepolizumab) had no baseline SNOT-22 score and was excluded from the analysis. (m)ITT, (modified) intent-to-treat; CI, confidence interval; CT, computerised topography; ITT, intent-to-treat; LMK, Lund–Mackay; LS, least squares; SC, subcutaneous; SE, standard error; SNOT-22, Sino-Nasal Outcome Test, 22 questions; VAS, visual analogue scale.

Discussion

The Phase III MERIT study demonstrated the efficacy and safety of mepolizumab in patients with CRSwNP/ECRS and NP in Japan, China, and Russia compared with placebo (both plus SoC). The co-primary endpoint change from baseline in nasal obstruction VAS score and all secondary endpoints demonstrated statistically significant benefits for patients treated with mepolizumab 100 mg subcutaneous compared with placebo. Improvements with mepolizumab versus placebo in the other co-primary endpoint, change from baseline in total ENPS at Week 52, did not reach statistical significance in the mITT population. Nonetheless, NP size was reduced from baseline, as evidenced by NP and LMK-CT scores.

Following study completion, the study sponsor was notified of GCP violations in other studies by an SMO managing two of the MERIT study sites. Thus post hoc analyses excluding the six patients from these two sites were conducted, enabling an assessment of the robustness of the study findings. It should be noted that no evidence of data falsification relating directly to the MERIT study was identified at these sites. In the mITT population, in which these six patients were excluded, there are small changes in efficacy effect sizes and a slight shift in the CIs, resulting in a p-value for the co-primary endpoint (change from baseline to Week 52 in total ENPS) that increased above the threshold of 0.05 (p=0.067 vs p=0.043 in the ITT population). Given p>0.05 for total ENPS in the mITT population, per the predefined hierarchy of endpoints, adjusted p-values could not be calculated for the secondary endpoints in the mITT population; as such, the unadjusted p-values presented should be interpreted with caution.

Importantly, a sensitivity analysis demonstrated that larger improvements in NP size and nasal obstruction were observed for the supplementary estimand in which patients who underwent sinus surgery or SCS use for CRSwNP/ECRS up to Week 52 were

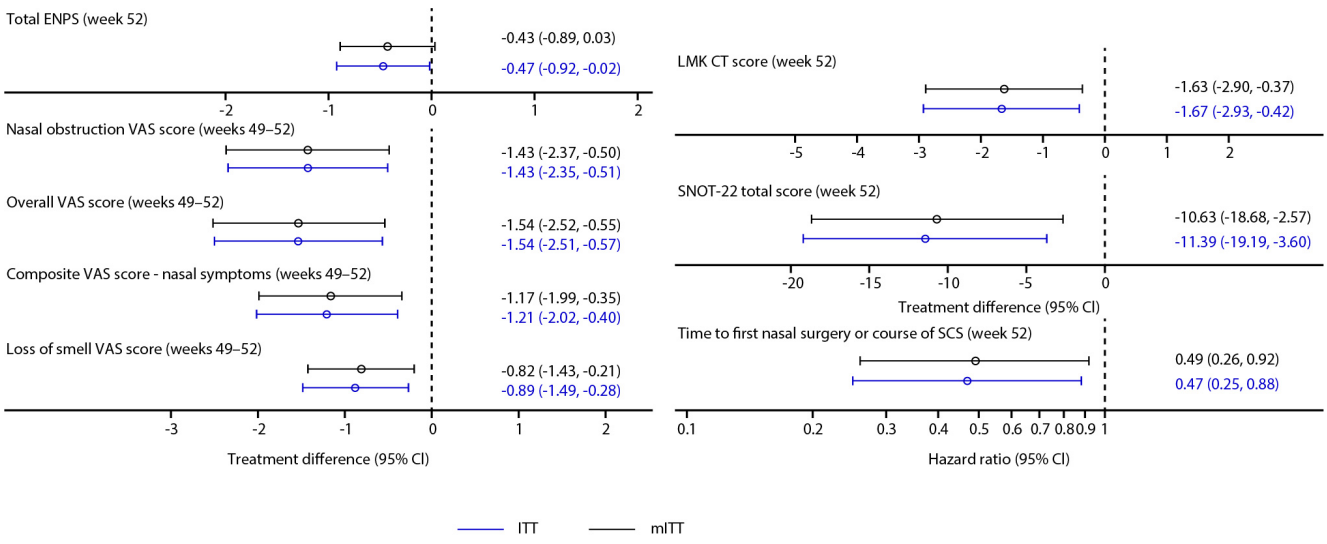

Figure 4. Forest plot of treatment difference/hazard ratio for primary and secondary endpoints for mITT and ITT populations. (m)ITT, (modified) intent-to-treat; CI, confidence interval; CT, computed tomography; ENPS, endoscopic nasal polyp score; LMK, Lund–Mackay; SCS, systemic corticosteroids; SNOT-22, Sino-Nasal Outcomes Test, 22 Questions; VAS, visual analogue score.

assigned the worst possible score for all subsequent visits.

All patients were required to have at least one of previous nasal surgery for NP, ≥3 consecutive days of SCS in the previous 2 years for the treatment of NP, or be medically unsuitable or intolerant to SCS. Most patients included in the study were using maintenance INCS at baseline and had previous surgeries; therefore, the results from this study suggest that mepolizumab treatment is efficacious in patients with severe disease. Additionally, all symptom scores, including loss of sense of smell, were significantly improved from baseline at Week 49–52 for patients treated with mepolizumab compared with placebo. Furthermore, patient sinonasal disease-specific QoL demonstrated improvements from baseline with mepolizumab versus placebo treatment, as demonstrated by reductions in SNOT-22 scores. Compared with placebo, mepolizumab also significantly increased the time to first sinus surgery or course of SCS. Finally, there were no new safety signals observed with mepolizumab, with a similar proportion of patients experiencing AEs. Overall, this study provides evidence of the benefit of mepolizumab in patients with CRSwNP/ECRS and NP further to previous studies of SC and intravenous mepolizumab [24, 32, 33].

Although the magnitude of improvement in total ENPS in the mITT population in MERIT (-0.43) was smaller than in SYNAPSE (-0.73) [24], and did not reach statistical significance for the reasons previously described, this reduction in NP size was still associated with improvements in symptoms and disease-specific QoL, as well as a reduced need for sinus surgery/SCS use. This is likely a reflection of an improvement in sinus inflammation as shown by LMK-CT scores, as well as reductions in blood eosinophil counts with mepolizumab. Higher blood eosinophil counts are associated with more severe and more refractory disease, in addition to more frequent disease recurrence than in patients with lower eosinophil counts [9-11].

A greater proportion of patients treated with mepolizumab compared with placebo achieved responder status for total ENPS and mean nasal obstruction VAS. Although the response in total ENPS was observed as early as Week 4, this response was only statistically significant from Weeks 29–32 for mean nasal obstruction VAS score. The results may suggest that although clinical measures indicate improvement very soon after treatment initiation, patients may require more time to feel the benefit of treatment and the related improved symptoms.

There was a higher rate of study withdrawal in the placebo (19%) compared with the mepolizumab (7%) group, largely driven by patient withdrawal and lack of efficacy, and generally consistent with withdrawal rates from the SYNAPSE study [24]. This may have influenced data for the remaining population at later timepoints. This is exemplified by improvements from baseline in SNOT-22 total score in the placebo group. As MERIT was conducted during the COVID-19 pandemic, this placebo effect may be partially due to reduced patient exposure to viruses, irritants, and/or aeroallergens [34, 35]. Indeed, one retrospective study of patients with CRS found that SNOT-22 scores were significantly higher, indicating more severe disease in the year before the pandemic compared with during the first year of the pandemic [36]. Another factor contributing to the improvements seen within the placebo group may have been the nearly two-thirds (58%) of patients in the mITT population receiving placebo who were using SCS in the 12 months prior to MERIT, higher than the 49% in the mepolizumab group. This may suggest that patients in the placebo group had slightly more severe CRSwNP/ECRS than patients in the mepolizumab, allowing for a

greater scope for improvements.

The results of MERIT are overall consistent with those reported in the Phase III SYNAPSE study, which investigated the efficacy and safety of mepolizumab in patients with CRSwNP [24]. They also expand on them, showing that further to the reductions in NP severity as shown by endoscopic assessment, NP severity is also reduced when assessed by CT scans. However, caution should be taken when interpreting differences in results from MERIT and SYNAPSE due to patient population differences, which may have impacted disease characteristics, particularly the proportion of patients that required surgery and differences in previous treatments at baseline. Patients in MERIT could have either previous sinus surgery, be an SCS user in the 2 years before enrolment, or be medically unstable or intolerant to SCS, whereas SYNAPSE required patients to have had ≥1 sinus surgery in the prior 10 years [24]. Consequently, only approximately 65% of patients in MERIT had a previous sinus surgery, compared with all patients in SYNAPSE. While inclusion of patients without prior sinus surgery was an intentional choice to broaden the potential study population (potentially extending the benefits of treatment to a larger population), the patient population of MERIT may therefore be closer in severity to that included in the LIBERTY NP SINUS and OSTRO studies of dupilumab and benralizumab, where 63% and 73% of patients had a prior sinus surgery, respectively [37, 38]. Additionally, MERIT enrolled patients who were not receiving background INCS, and its eligibility criteria were partly based on JESREC criteria for ECRS [9]. This included criteria such as having a CT shadow, the presence of comorbidities (AERD and asthma), and a blood eosinophil count (>2%). However, it should be noted that despite the blood eosinophil criteria, baseline eosinophil counts were similar in both the SYNAPSE and MERIT studies [24].

Beyond the SYNAPSE study, the results of MERIT are generally consistent with the clinical benefits of other Type 2 inflammation targeting biologics, including dupilumab and benralizumab in the LIBERTY NP SINUS and OSTRO clinical studies [37, 38], both of which did not require patients to have a history of sinus surgery. With dupilumab, a subanalysis of the LIBERTY NP SINUS study found consistent clinical benefits in subgroups of patients based on JESREC criteria, with statistically non-significant but numerically greater increases in treatment effect with increasing JESREC disease severity [39]. However, results for benralizumab beyond the OSTRO study have been less consistent, with a Phase II trial of patients with ECRS in Japan finding no significant reduction in NP score with benralizumab versus placebo, although the study did note a trend for numerically greater treatment effects with increasing blood eosinophil count [40]. This trend is consistent with a subgroup analysis of SYNAPSE, where clinical benefit with mepolizumab versus placebo was observed regardless of comorbid asthma or AERD, and baseline blood eosinophil count, but with greater treatment effects in patients with ≥150 and ≥300 cells/μL than counts lower than these thresholds [41].

Improvements in disease outcomes with CRSwNP biologics have also been observed in real-world studies, both where treatment effects are assessed across all available treatment options [42-46], and for individual treatments including mepolizumab and dupilumab [47-49]. It is notable in these real-world studies that improvements in ENPS and SNOT-22 total scores are larger than those observed in clinical studies. Domínguez-Sosa, et al. observed a 4- and 63-point median decrease in NP score and SNOT-22 total score after 24 weeks of mepolizumab treatment, from baselines of 4 and 76 points, respectively [48]. By comparison, decreases in NP score and SNOT-22 total score in MERIT were 0.5 and 11 points, respectively. These differences may reflect the less stringent criteria typically used in real-world compared with clinical studies.

This study has several limitations, which should be considered when interpreting the results. First, MERIT was a regional study; therefore, the results may not be generalisable to a global population, particularly as recent research suggests there may be differences in the proportion of inflammation types in Asia compared with Europe [26], and there may also be differences in endotypes and environmental factors between these populations. Further, the sample size was approximately one-third that of SYNAPSE. Additionally, patient population differences between MERIT and SYNAPSE are important considerations when interpreting study results. Finally, the MERIT study timeframe (conducted during COVID-19) adds another potential complexity. However, through careful study design and analysis of outcomes, and the absence of direct COVID-19-related treatment discontinuations or participant withdrawals (and only two participants requiring changes in background medication due to COVID-19), we remain confident that the overall impact of the pandemic on the study's outcomes was relatively minimal.

Conclusion

In Japan, China, and Russia, mepolizumab treatment reduced nasal obstruction and sinonasal symptoms, in addition to improving sinonasal disease-specific QoL, compared with placebo. The safety profile of mepolizumab was acceptable and consistent with previous reports. Overall, these efficacy and safety data from MERIT and the consistency in the effect size estimates for the co-primary and secondary efficacy outcomes between the pre-specified and post hoc analyses support a positive benefit-risk profile for mepolizumab in patients with inadequately controlled CRSwNP/ECRS and NP from Japan, China, and Russia.

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Authorship contribution

SF, AF, LS, ES, ARS, RC, and LZ contributed to the study conception or design, SF, CW, MY, MA, IS, and LZ contributed to the acquisition of data, AF, LS, ES, AS, and RC contributed to data analysis, and all contributed to the data interpretation, development of the manuscript, and approval of the final draft to be published. All authors reviewed and revised the manuscript critically for important intellectual content, agreed to submit to the current journal, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work. All authors had access to the study data.

Conflict of interest

SF declares research support from Sanofi, Mitsubishi Tanabe Pharma Corporation, KYORIN Pharmaceutical Co., Ltd, and GSK; CW received consulting fees from GSK, speaker fees from Sanofi and AstraZeneca, and research grants from Novartis; MY has received lecture fees from Sanofi and research funding from Kissei Pharmaceutical; MA declares research contracts with GSK, AstraZeneca, and Sanofi and presentation fees from GSK, AstraZeneca, Sanofi, Kyoryn, and Taiho; IS has received speaker fees and a research grant from Sanofi; CB has participated in advisory boards and received speaker fees from AstraZeneca, Sanofi, Novartis, and GSK; JKH has received consultancy fees from Sanofi Genzyme, Regeneron, Genentech, AstraZeneca, and GSK; AF is a contract resource for GSK; LB is a former employee of GSK; LS, ES, ARS, and RC are employees of GSK and LS, ARS, and RC own stocks/shares; LZ declares no conflicts of interest.

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The sponsor was involved in study design and implementation, as well as data collection, analysis, interpretation, writing the study report and reviewing this manuscript. The sponsor did not place any restrictions on access to data or statements made in the manuscript. All authors had full access to the data upon request and had final responsibility for the decision to submit for publication.

Data sharing statement

Please refer to GSK weblink to access GSK's data sharing policies and as applicable seek anonymised subject level data via the link https://www.gsk-studyregister.com/en/ (GSK ID: 209692).

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Professor L. Zhang
Department of Otolaryngology
Head and Neck Surgery
and Department of Allergy
Beijing TongRen Hospital
Capital Medical University
No.1, Dongjiaominxiang
DongCheng District
Beijing 100730
P.R. China 100051

Tel: (+8610) 5826 5719/
(+8610) 6526 4431
E-mail: dr.luozhang@139.com

Shigeharu Fujieda[1], Chengshuo Wang[2], Mamoru Yoshikawa[3], Mikiya Asako[4], Isao Suzaki[5], Claus Bachert[6], Joseph K. Han[7], Abby Fuller[8,9], Lee Baylis[10], Lin Su[11], Eri Sasaki[12], Ana R Sousa[13], Robert Chan[13], Luo Zhang[2]

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[1] Department of Otorhinolaryngology, Head & Neck Surgery, University of Fukui, Japan
[2] Department of Otolaryngology, Head and Neck Surgery, Beijing TongRen Hospital, China
[3] Department of Otorhinolaryngology, Toho University Ohashi Medical Centre, Japan
[4] Department of Otolaryngology, Kansai Medical University, Japan
[5] Department of Otorhinolaryngology, Head and Neck Surgery, Showa University, Japan
[6] ENT Department, University of Münster, Germany
[7] Department of Otolaryngology - Head and Neck Surgery, Eastern Virginia Medical School, USA
[8] Clinical Statistics, GSK, GSK House, Brentford, UK
[9] Veramed Ltd, Twickenham, UK
[10] Global Medical Affairs, Specialty Care, GSK, Durham, NC, USA*
[11] Clinical Development, Respiratory, GSK, Shanghai, China
[12] Clinical Development (Respiratory), Respiratory Medical Affairs & Development, GSK Japan, Tokyo, Japan
[13] Clinical Sciences, Respiratory, GSK, Brentford, Middlesex, UK

* At time of study

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Ahmad Sedaghat

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. LS mean change from baseline in total ENPS at Week 52 by baseline BEC subgroup.

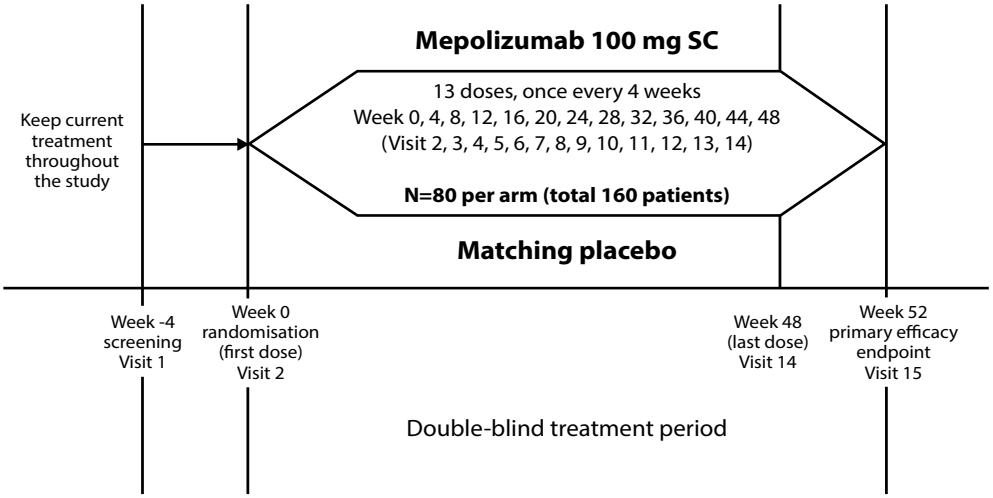
	mITT					
	Baseline BEC <5%		**Baseline BEC ≥5–<10%**		**Baseline BEC ≥10%**	
	Mepolizumab 100 mg SC (n=25)	Placebo (n=21)	Mepolizumab 100 mg SC (n=36)	Placebo (n=40)	Mepolizumab 100 mg SC (n=19)	Placebo (n=22)
LS mean change (SE)	-0.46 (0.27)	0.06 (0.294)	-0.63 (0.27)	-0.31 (0.26)	-0.79 (0.29)	-0.30 (0.29)
Difference (mepolizumab–placebo) (95% CI)	-0.52 (-1.35, 0.30)		-0.32 (-1.08, 0.44)		-0.49 (-1.35, 0.37)	
	ITT					
	Baseline BEC <5%		**Baseline BEC ≥5–<10%**		**Baseline BEC ≥10%**	
	Mepolizumab 100 mg SC (n=26)	Placebo (n=23)	Mepolizumab 100 mg SC (n=39)	Placebo (n=40)	Mepolizumab 100 mg SC (n=19)	Placebo (n=22)
LS mean change (SE)	-0.49 (0.26)	0.09 (0.28)	-0.72 (0.26)	-0.30 (0.26)	-0.79 (0.29)	-0.30 (0.29)
Difference (mepolizumab–placebo) (95% CI)	-0.57 (-1.35, 0.21)		-0.42 (-1.16, 0.33)		-0.49 (-1.35, 0.37)	

(m)ITT, (modified) intent-to-treat; BEC, blood eosinophil count; CI, confidence interval; ENPS, endoscopic nasal polyp score; LS, least squares; SC, subcutaneous; SE, standard error.

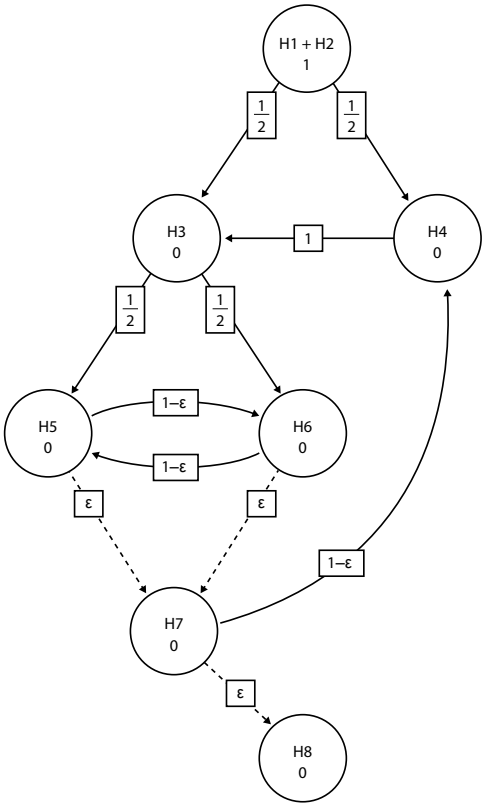
Supplementary Table 2. Summary of AEs (safety population).

	Mepolizumab 100 mg SC (N=84)	Placebo (N=85)
All AEs, n (%)		
Any on-treatment event	68 (81)	65 (76)
Treatment-related event	2 (2)	5 (6)
Leading to permanent discontinuation of study treatment	0 (0)	2 (2)
Leading to study withdrawal	0 (0)	2 (2)
Most common AEs*, n (%)		
COVID-19	15 (18)	15 (18)
Nasopharyngitis	7 (8)	9 (11)
Headache	6 (7)	6 (7)
Back pain	3 (4)	5 (6)
Immunization reaction	5 (6)	3 (4)
Dizziness	2 (2)	5 (6)
Pyrexia	3 (4)	4 (5)
Asthma	1 (1)	5 (6)
Hypertension	2 (2)	4 (5)
Post-vaccination fever	2 (2)	4 (5)
SAEs, n (%)		
Any on-treatment event	0 (0)	4 (5)
Treatment-related event	0 (0)	0 (0)
Fatal	0 (0)	0 (0)
AEs of special interest, n (%)		
Allergic (Type 1 hypersensitivity)	0 (0)	1 (1)
Local site reactions	0 (0)	2 (2)
All infections	37 (44)	35 (41)
Potential opportunistic infections	1 (1)	1 (1)
Neoplasms † and malignancies ‡	0 (0)	1 (1)
Cardiac disorders	1 (1)	1 (1)

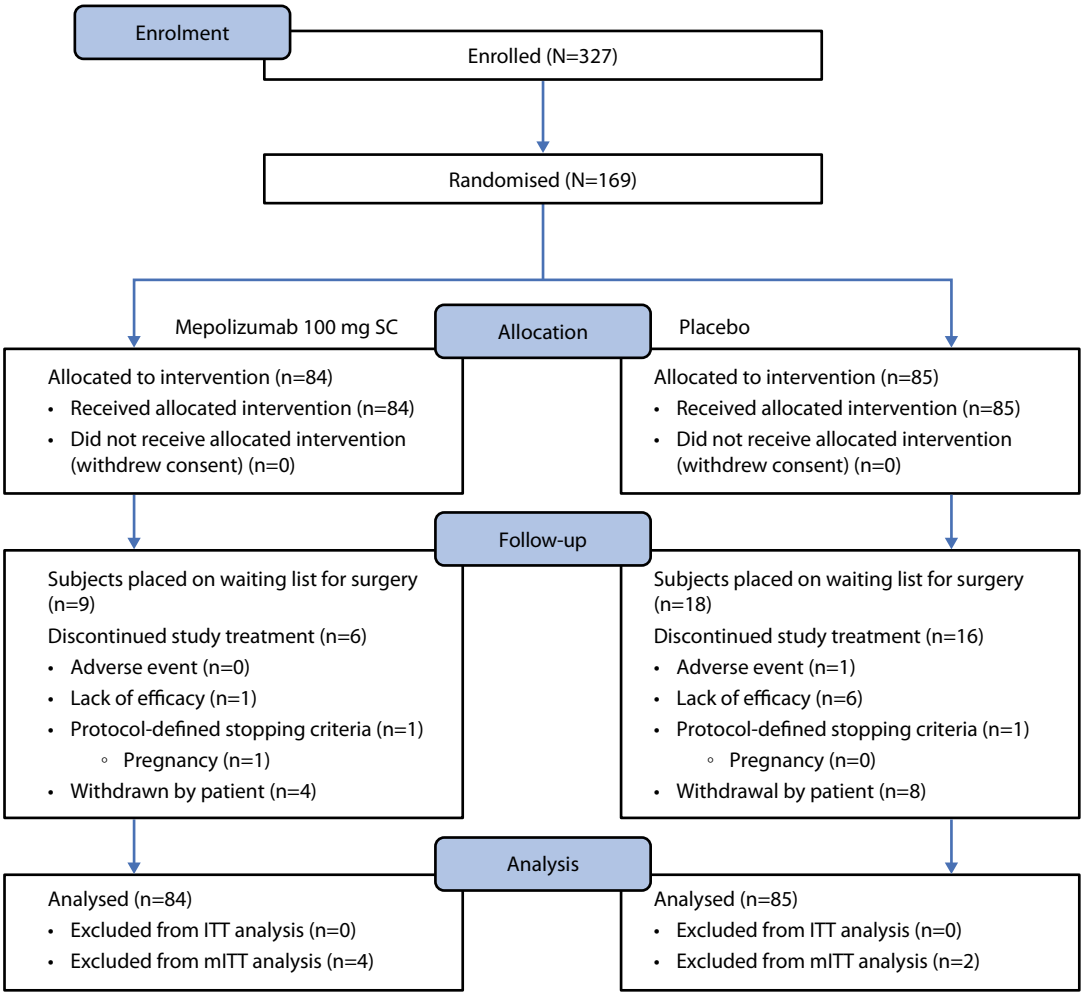
* Reported ≥5% of patients in any treatment group; † based on System Organ Coding; ‡ Based on the Standardised MedDRA Queries. AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SC, subcutaneous.



Supplementary Figure 1. MERIT study design.
SC, subcutaneous.

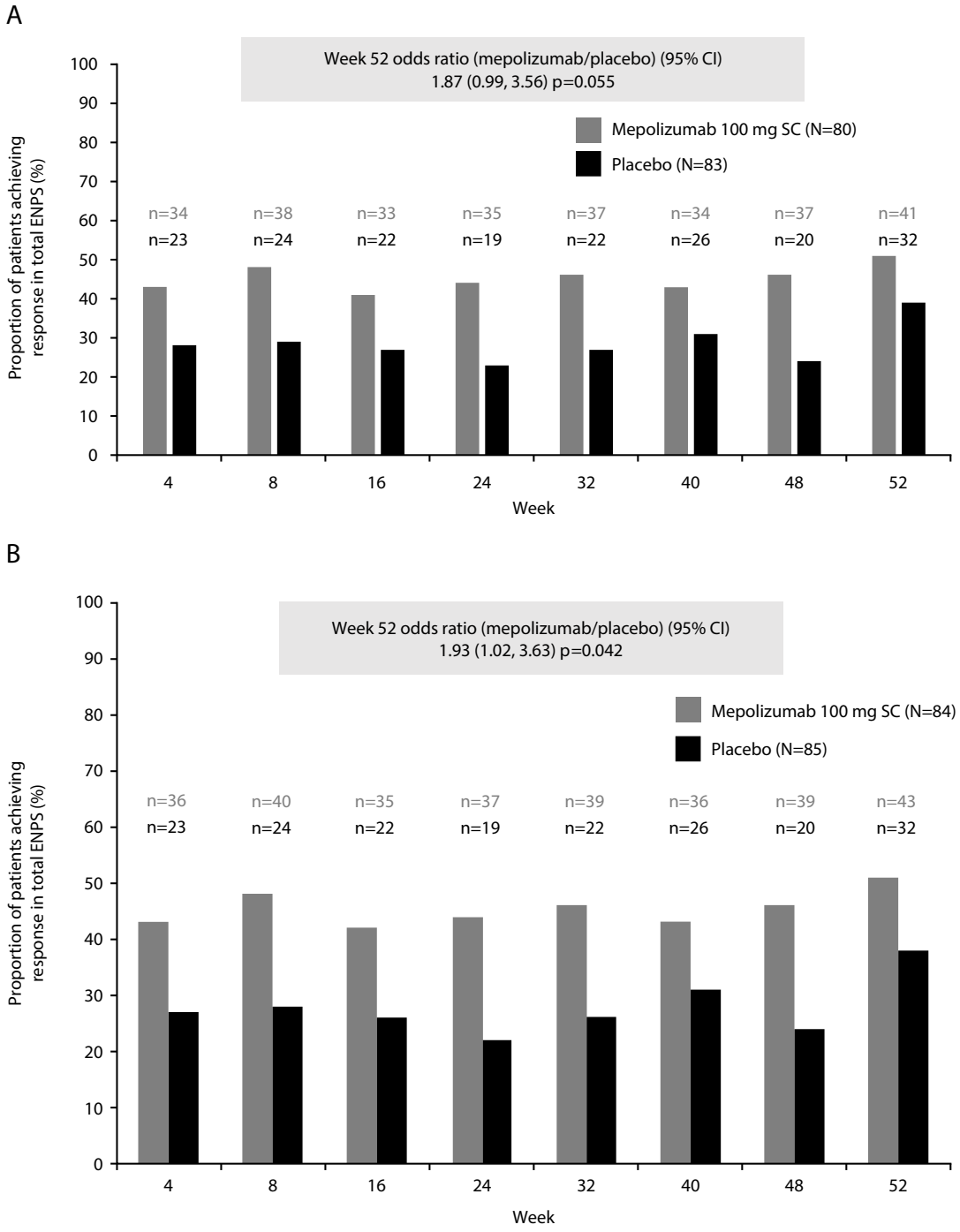


Supplementary Figure 2. Pre-defined hierarchy of endpoints.
Primary endpoints: Total ENPS (H1) and nasal obstruction VAS score during the 4 weeks prior to Week 52 (H2). Secondary endpoints: Overall VAS score during the 4 weeks prior to Week 52 (H3), LMK-CT score at Week 52 (H4), composite VAS score of nasal symptoms prior to Week 52 (H5), SNOT-22 total score at Week 52 (H6), loss of smell VAS score during the 4 weeks prior to Week 52 (H7), time to first nasal surgery or course of SCS for CRSwNP up to Week 52 (H8). ε represents an infinitesimally small value, indicating the potential for α to be reallocated dependent on the rejection of all previous tests. CRSwNP, chronic rhinosinusitis with nasal polyps; CT, computed tomography; ENPS, endoscopic nasal polyp score; H, hypothesis; LMK, Lund–Mackay; SCS, systemic corticosteroid; SNOT-22, Sino-Nasal Outcome Test, 22 questions; VAS, visual analogue scale.

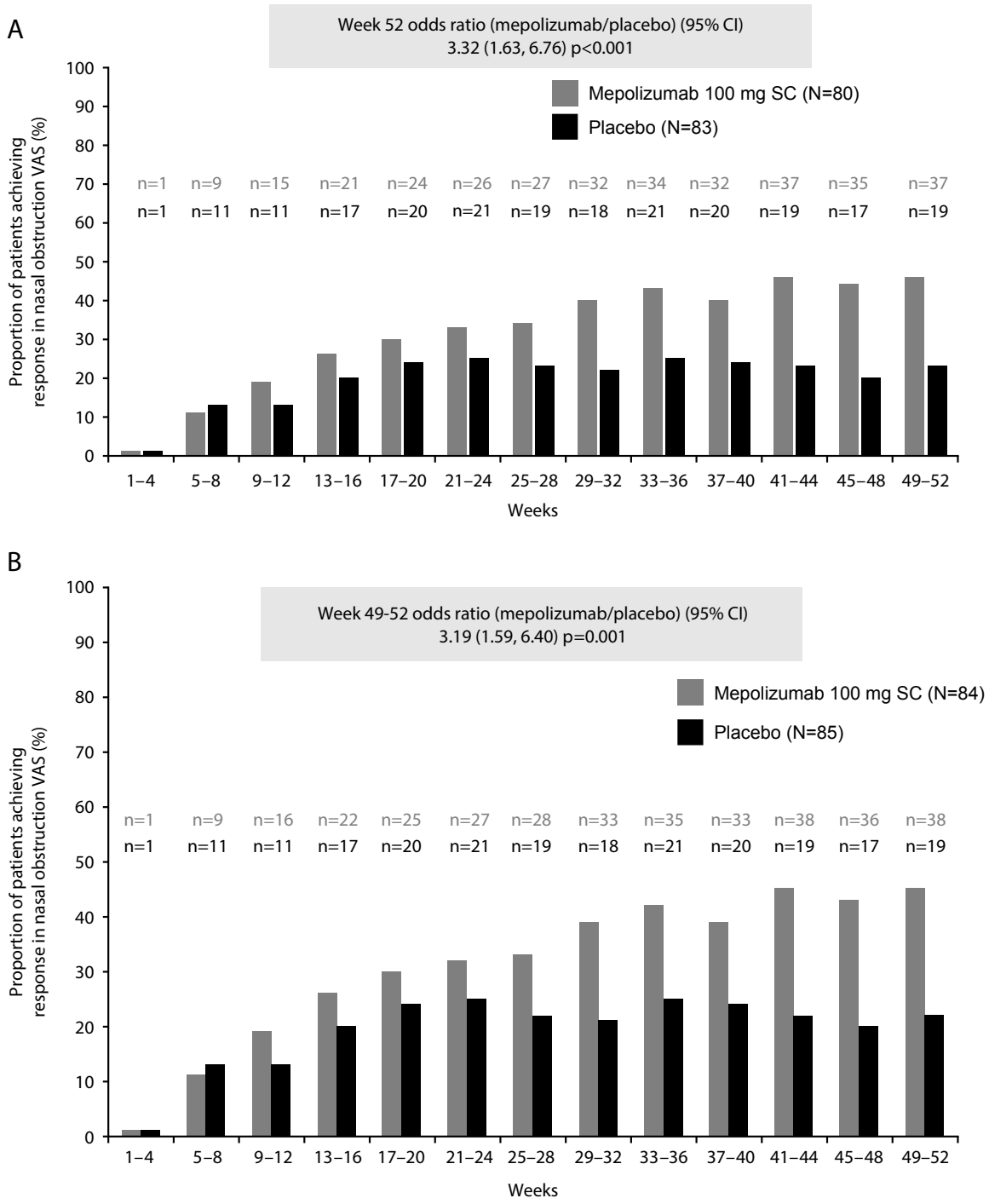


Supplementary Figure 3. Patient disposition.

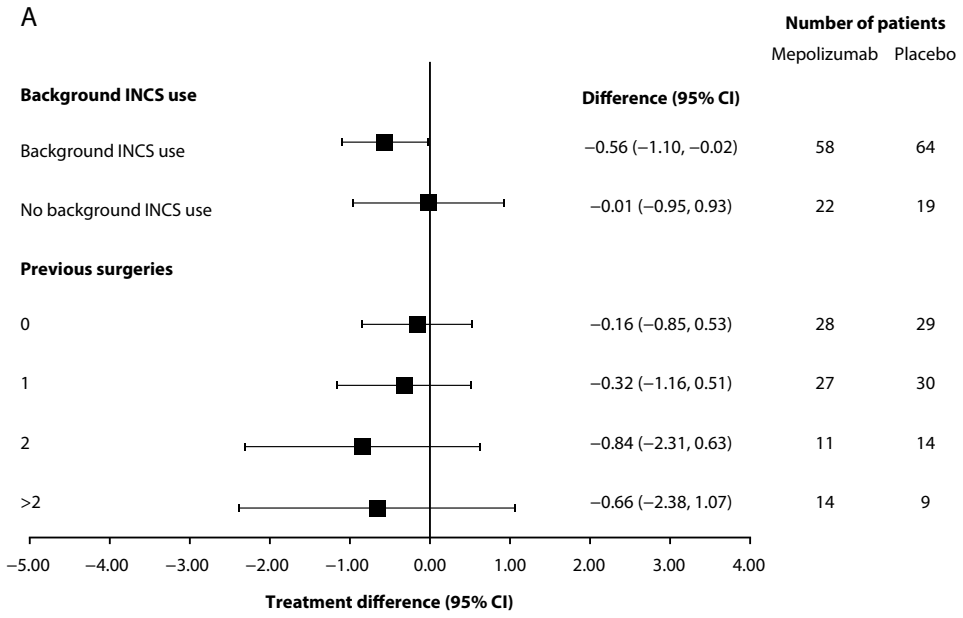
SC, subcutaneous.

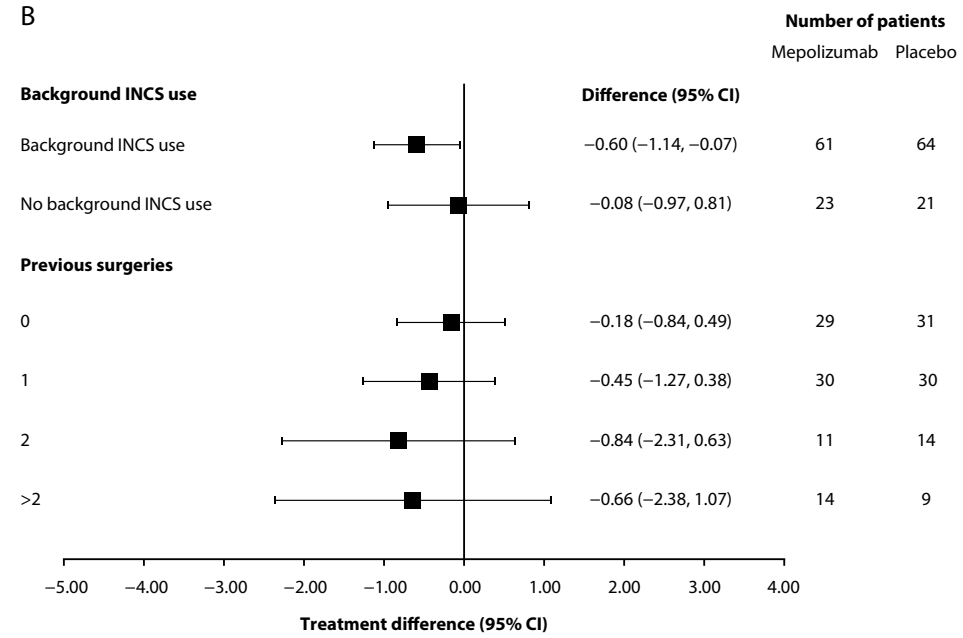


Supplementary Figure 4. The proportion of patients achieving responder status in total ENPS in the (A) mITT and (B) ITT population.
Response was defined as a patient achieving ≥1-point improvement (decrease) from baseline in total endoscopic NP score at the week of measurement, in the absence of surgery prior to visit.
n=number of responders. (m)ITT, (modified) intent-to-treat; CI, confidence interval; ENPS, endoscopic nasal polyp score; NP, nasal polyp; SC, subcutaneous.

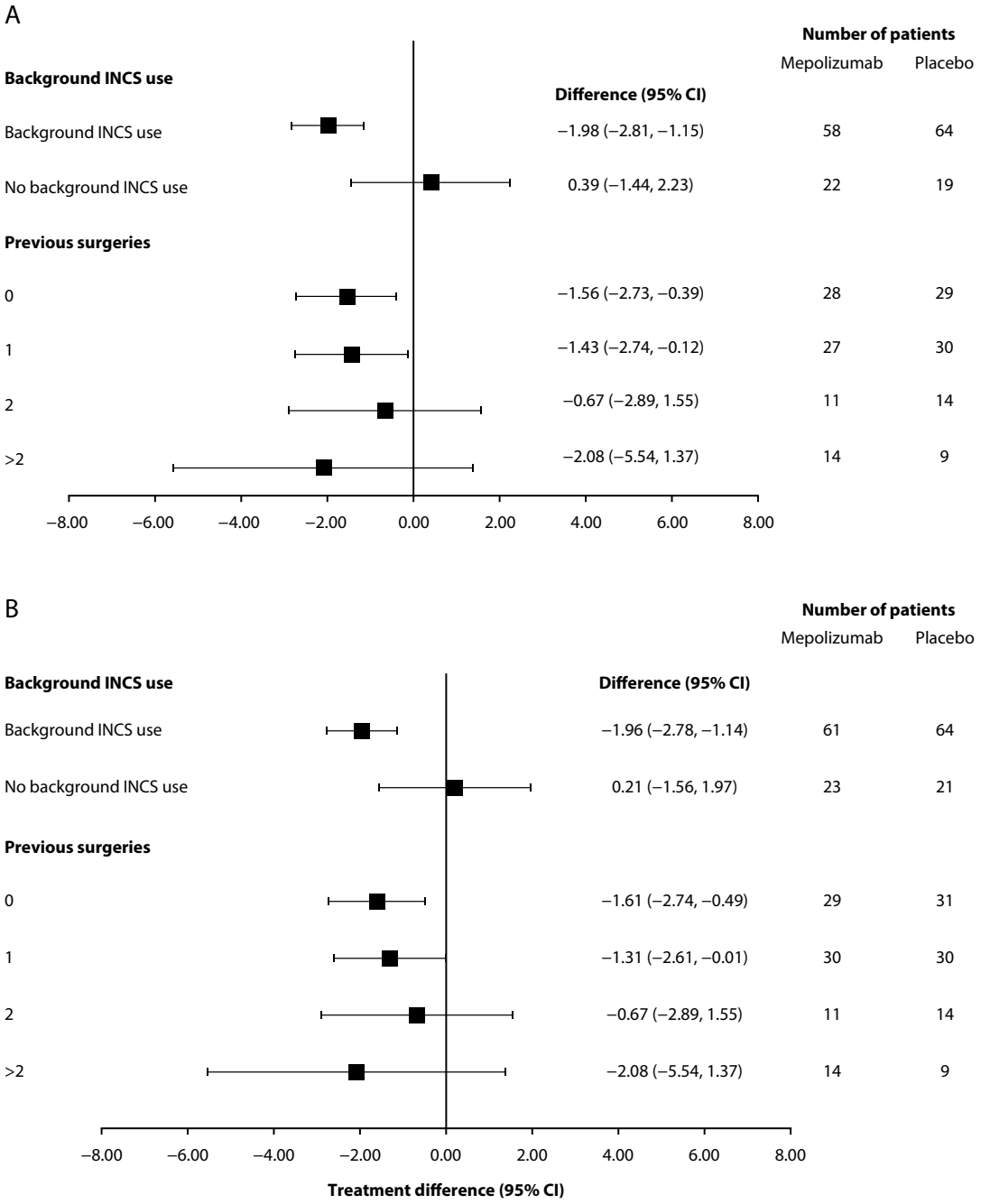


Supplementary Figure 5. The proportion of patients achieving responder status in VAS nasal obstruction in the (A) mITT and (B) ITT population. A >3-point improvement from baseline in nasal obstruction VAS at the week of measurement, in the absence of prior surgery. n=number of responders. (m)ITT, (modified) intent-to-treat; CI, confidence interval; SC, subcutaneous; VAS, visual analogue scale.



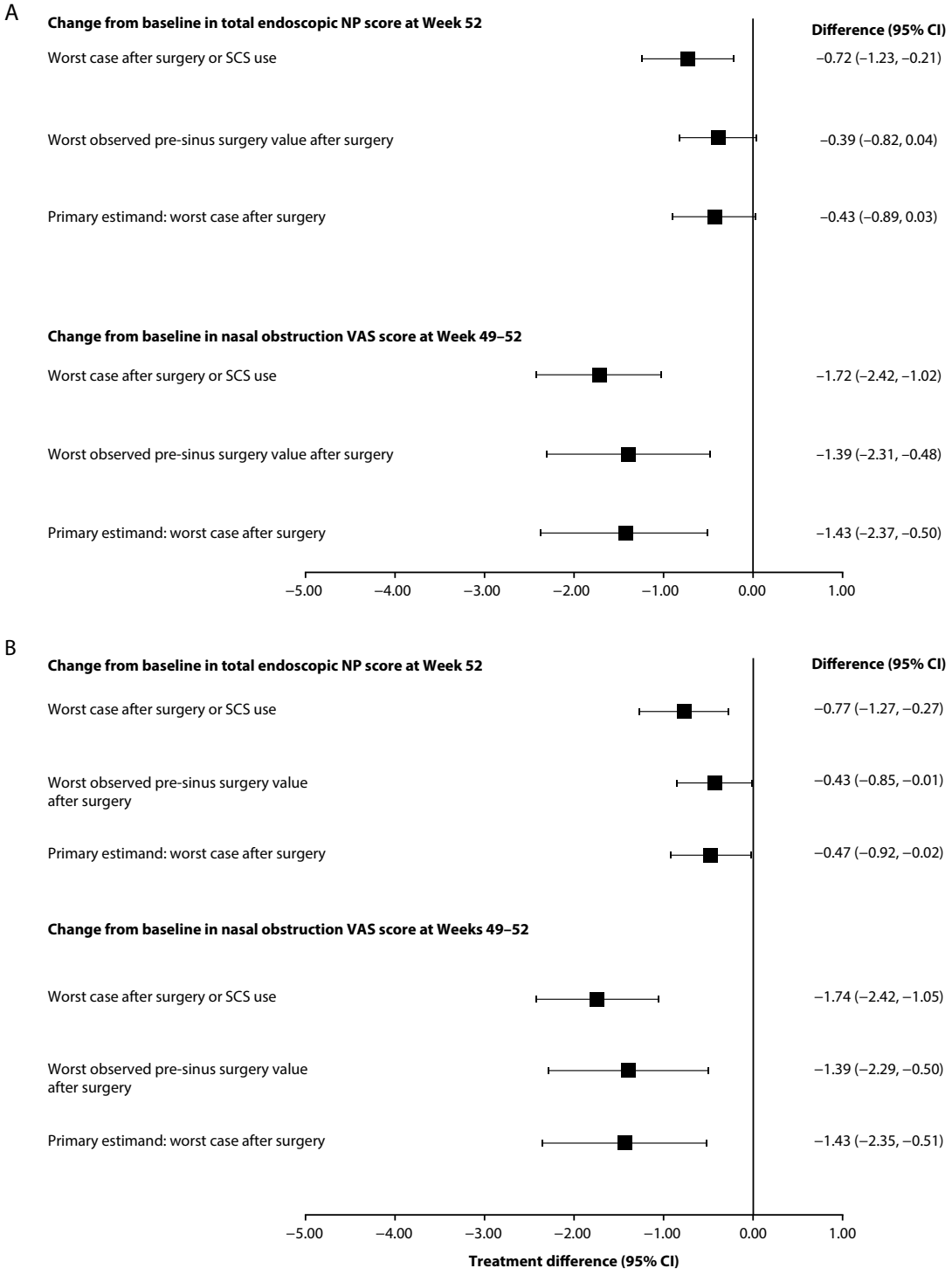


Supplementary Figure 6. Effect of background INCS use and previous history of surgery on NP score in the (A) mITT and (B) ITT population.
CI, confidence interval; INCS, intranasal corticosteroid; NP, nasal polyps; VAS, visual analogue scale.



Supplementary Figure 7. Effect of background INCS use and previous history of surgery on VAS nasal obstruction score in the (A) mITT and (B) ITT population.

(m)ITT, (modified) intent-to-treat; CI, confidence interval; INCS, intranasal corticosteroids; VAS, visual analogue scale.



Supplementary Figure 8. Sensitivity analyses of the co-primary endpoints in the (A) mITT and (B) ITT population.
CI, confidence interval; (m)ITT, (modified) intent-to-treat; NP, nasal polyps; SCS, systemic corticosteroid; VAS, visual analogue scale.