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Mepolizumab improves sense of smell in severe chronic rhinosinusitis with nasal polyps: SYNAPSE*

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Abstract

Background: Loss of smell is one of the most bothersome and difficult-to-treat symptoms in patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP).

Methodology: SYNAPSE was a 52-week Phase III study of 4-weekly mepolizumab (100 mg subcutaneously) plus standard of care in adults with severe bilateral CRSwNP. This post hoc analysis assessed changes from baseline to study end in loss of smell visual analogue scale (VAS) symptom score, in patients stratified by several baseline clinical characteristics. SinoNasal Outcomes Test (SNOT)-22 sense of smell/taste item and University of Pennsylvania Smell Identification Test (UPSIT) scores were also assessed.

Results: SYNAPSE enrolled 407 patients (mepolizumab=206; placebo=201) with impaired sense of smell at baseline. Improvements from baseline to study end in loss of smell VAS score were greater with mepolizumab versus placebo (treatment difference: −0.37) and most notable in patients with fewer or more recent prior surgeries (treatment difference: 1 vs 2 vs >2 prior surgeries, −1.29 vs −0.23 vs −0.07; <3 vs ≥3 years since last surgery, −0.89 vs 0.22). Approximately 25% of patients had baseline UPSIT scores available; among those scoring <19, 14–20% in both treatment arms achieved scores ≥19 by study end. The SNOT-22 sense of smell/taste item score improved with mepolizumab versus placebo.

Conclusions: Mepolizumab treatment improved patients' perceived sense of smell, as measured by loss of smell VAS score and SNOT-22 sense of smell/taste item score in patients with severe refractory CRSwNP.

Key words: biological treatment, chronic rhinosinusitis, nasal polyps, smell

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterised by chronic inflammation of the paranasal sinuses, resulting in the formation of nasal polyps [1-3]. In the US, up to 87% of CRSwNP cases involve eosinophilic inflammation, which has been attributed to loss of smell. Similarly, in a recent epidemiological study including data from 30,000 patients in Spain, 87% of patients with severe CRSwNP had type 2 inflammation; this reached 91% when associated with respiratory comorbidities [2, 4]. Patients with CRSwNP experience a range of symptoms, including nasal blockage, rhinorrhoea, loss of smell, and facial pressure, which can have a substantial impact on health-related quality of life (HRQoL) [5-8]. Loss of smell is one of the most bothersome and difficult-to-treat symptoms [9], correlates with

disease severity [10], and is associated with type 2 inflammation[2]. In addition to its substantial impact on HRQoL, loss of smell may also have significant effects on psychological health, including higher levels of anxiety, phobia, and depression [11].

Current standard of care (SoC) for CRSwNP includes intranasal corticosteroids, short courses of systemic corticosteroids (SCS) and sinus surgery [12]. Biologic agents that target type 2 inflammatory cytokines such as interleukin (IL)-5, IL-4, and IL-13, and immunoglobulin E, are now available and are recommended for use in patients with the most severe disease [12]. Factors associated with very severe CRSwNP include previous sinus surgery, a need for SCS, significantly impaired HRQoL, significant loss of smell, a diagnosis of comorbid asthma and/or nonsteroidal anti-inflammatory drug exacerbated respiratory disease, and evidence of type 2 inflammation [13-15]. Mepolizumab is a humanised monoclonal antibody that binds to and inactivates IL-5, thereby blocking the proliferation, activation, and survival of eosinophils [16]. Elevated levels of eosinophils and IL-5 have been implicated in the pathogenesis of CRSwNP. In the United States (US) and Europe, mepolizumab is approved as an add-on treatment for severe eosinophilic asthma, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, and CRSwNP [17,18]. In the Phase III SYNAPSE study, mepolizumab significantly improved sinonasal symptoms in patients with recurrent severe CRSwNP despite current optimal medical management and prior sinus surgery, compared with placebo[19]. Patients also demonstrated a reduced need for repeat sinus surgery, and modest improvements in their sense of smell with mepolizumab versus placebo, as demonstrated by change from baseline in loss of smell visual analogue scale (VAS) score during Weeks 49–52 (a secondary endpoint) [19]. This post hoc analysis of the SYNAPSE study aimed to describe the impact of recurrent severe CRSwNP on sense of smell, and to more fully assess the impact of mepolizumab on patients' loss of smell, in addition to further characterising those patients whose olfaction improved with mepolizumab.

Materials and methods

Study design and patient eligibility

SYNAPSE (GSK ID: 205687; NCT03085797) was a Phase III randomised, double-blind, placebo-controlled, parallel-group, multicentre, 52-week study. The full SYNAPSE study design and patient eligibility criteria have been described in detail previously [19]. Briefly, following a 4-week run-in period, patients were randomised (1:1) to receive mepolizumab 100 mg subcutaneously (SC) or placebo, every 4 weeks for 52 weeks. Patients continued to receive SoC treatment throughout the study, which included daily mometasone furoate nasal spray and (if required) saline nasal douching, short courses of high-dose oral corticosteroids (OCS), and/or antibiotics. 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 and the study was approved by local ethics review boards at participating sites. The protocol is available at https://www.gsk-studyregister.com/.

SYNAPSE enrolled patients ≥18 years of age with recurrent, refractory, severe bilateral nasal polyps (NP), as defined by a nasal obstruction VAS score >5 (maximum 10; see Supplementary Section 1) and a need for repeat sinus surgery (overall symptoms VAS score >7 and endoscopic NP score ≥5 [maximum 8], with a NP score ≥2 in each nasal cavity) despite receiving optimised SoC treatment. All eligible patients had undergone sinus surgery (defined as any surgery of the paranasal sinuses with resulting nasal polypectomy) in the last 10 years and had been receiving stable maintenance therapy with intranasal mometasone furoate spray for ≥8 weeks before screening. Patients also displayed ≥2 different symptoms including nasal blockage/obstruction/congestion and/or nasal discharge (anterior or posterior nasal drip) for ≥12 weeks before screening, along with a reduction in or complete loss of smell and/or facial pain or pressure (in line with the European Position Paper on Chronic Rhinosinusitis and Nasal Polyps definition of rhinosinusitis in adults [13]).

Endpoints and assessments

Sense of smell-related patient characteristics were assessed at baseline, including: mean loss of smell VAS score (previously reported [19]); mean SinoNasal Outcomes Test (SNOT)-22 sense of smell/taste item score; mean University of Pennsylvania Smell Identification Test (UPSIT) score; the proportion of patients with VAS-defined normal sense of smell/mild hyposmia (loss of smell VAS score 1–3), moderate hyposmia (loss of smell VAS score >3–7) or severe hyposmia/anosmia (loss of smell VAS score >7–10); and the proportion of patients with UPSIT-defined anosmia (UPSIT score <19) or no anosmia (UPSIT score ≥19). Baseline mean loss of smell VAS scores were summarised in patients with UPSIT-defined anosmia or no anosmia at baseline, to further characterise loss of smell in the population and to check for consistency between the two measures.

To assess the impact of baseline characteristics on loss of smell–related treatment response, median changes from baseline to Weeks 49–52 in loss of smell VAS score with mepolizumab versus placebo were assessed by number of surgeries in the prior year (1, 2, >2; pre-specified analysis, previously reported [19]), and post hoc by time since last surgery prior to study enrolment (<3 years, ≥3 years; based on the results of previous surgery recency analyses in patients with CRSwNP receiving biologic treatment [19]), and baseline blood eosinophil count (<150 cells/μL, ≥150 cells/μL, <300 cells/μL, ≥300 cells/μL). Median improvements in loss of smell VAS score were summarised according to baseline disease severity, as indicated by baseline SNOT-22 total

Table 1. Sense of smell specific patient characteristics at baseline.

	Placebo (N=201)	Mepolizumab (N=206)
Loss of smell VAS score (scale: 0–10), mean (SD)	9.7 (0.60)	9.6 (0.83)
n	201	206
Proportion of patients with VAS-defined severe hyposmia/anosmia (loss of smell VAS score >7–10), n (%)	200 (99.5)	205 (99.5)
Proportion of patients with VAS-defined moderate hyposmia (loss of smell VAS score >3–7), n (%)	1 (<1)	0
Proportion of patients with VAS-defined normal sense of smell/mild hyposmia (loss of smell VAS score 1–3), n (%)	0	1 (<1)
UPSIT score (scale: 0–40), mean (SD)	13.4 (7.45)	13.0 (6.81)
n	54	54
Proportion of patients with UPSIT-defined anosmia (UPSIT score <19), n (%)	43 (80)	46 (85)
Proportion of patients with UPSIT-defined hyposmia/normosmia (UPSIT score ≥19), n (%)	11 (20)	8 (15)
Loss of sense of smell/taste SNOT-22 item score (scale: 0–5), mean (SD)	4.8 (0.50)	4.7 (0.78)
n	198	205
Proportion of patients, n (%), rating their loss of sense of smell/taste as:		
No problem	0	2 (<1)
Very mild problem	0	2 (<1)
Mild or slight problem	0	1 (<1)
Moderate problem	7 (4)	5 (2)
Severe problem	32 (16)	36 (18)
Problem as bad as it could be	159 (80)	159 (78)

SD, standard deviation; SNOT-22, Sino-Nasal Outcomes Test-22; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analogue scale.

score (≤50, >50). To identify any potential relationships between loss of smell improvements and OCS dependence, median changes from baseline to Weeks 49–52 in loss of smell VAS score with mepolizumab versus placebo were also assessed by number of OCS courses during the study (0, 1, 2, ≥3). With regards to alternative measures of olfactory function, the proportions of patients with UPSIT-defined anosmia (UPSIT score <19) at baseline who had no anosmia (UPSIT score ≥19) or remained anosmic at Week 52 were summarised and median changes from baseline to Week 52 in the SNOT-22 sense of smell/taste item score (which does not differentiate between retronasal and orthonasal olfaction) were analysed post hoc.

Finally, to describe the clinical characteristics of patients with or without olfactory improvements during SYNAPSE, the proportions of patients identified as loss of smell VAS score responders (≥3-point improvement) and nonresponders (<3-point improvement) at Week 52 were reported, and baseline disease characteristics were summarised for both responder subgroups. The proportions of patients with UPSIT-defined anosmia (UPSIT score <19) and without UPSIT-defined anosmia (UPSIT score ≥19) at Week 52 were also summarised, and baseline disease characteristics were described for both subgroups.

Sample size and statistical analysis

All data reported up to Week 52 were included in the analysis, regardless of treatment discontinuation. Sample size calculations have been described previously [19]. Patients who underwent sinus surgery before Week 52 were assigned their worst observed score before surgery, for all subsequent visits. Patients who withdrew early from the study without having undergone sinus surgery or who had missing data for any other reason were assigned their worst observed score. The use of SCS during the treatment period was considered a part of SoC therapy; therefore, observed scores following SCS use were included in the analyses.

Change from baseline in loss of smell VAS score was analysed using quantile regression with covariates of treatment group, geographic region, baseline score, and $\log_e$ baseline blood eosinophil count. Proportion of loss of smell VAS score responders was analysed using a logistic regression model with covariates of treatment group, geographical region, and $\log_e$ baseline blood eosinophil count. All other analyses were descriptive. All data were analysed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

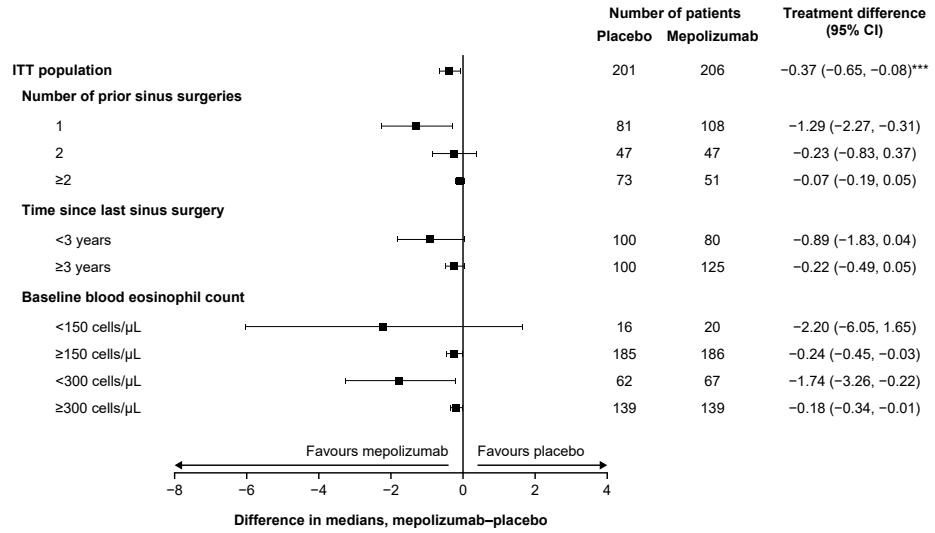

Figure 1. Median change from baseline in loss of smell VAS score at Weeks 49–52 by number of prior surgeries, time since last surgery, and baseline blood eosinophil count. ***p<0.001. CI, confidence interval; ITT, intent-to-treat; VAS, visual analogue scale.

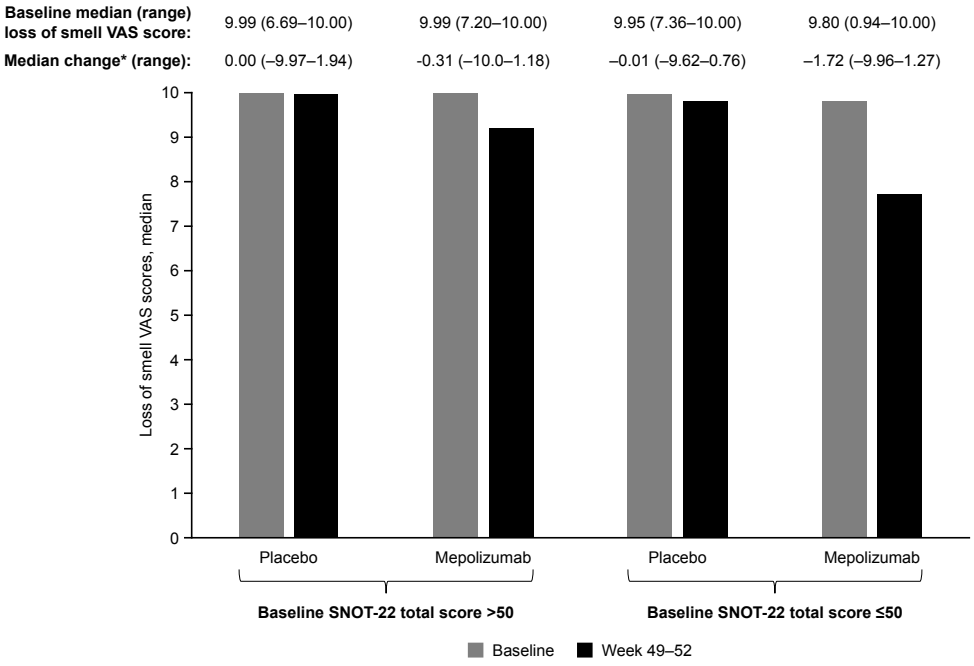

Figure 2. Loss of smell VAS scores by baseline SNOT-22 total score. *Baseline to Week 49–52. SNOT-22, SinoNasal Outcomes Test-22; VAS, visual analogue scale.

Results

Patient population

Overall, 407 patients (placebo: n=201; mepolizumab: n=206) were included in the SYNAPSE intent-to-treat (ITT) population [19]. Patient demographics and baseline characteristics have been described previously [19]; those specific to patients' sense of smell are reported in Table 1. Patients had a substantially impaired sense of smell at study screening, as indicated by mean (standard deviation [SD]) baseline loss of smell VAS scores of 9.68 (0.596) and 9.63 (0.830) out of 10 in the placebo and mepolizumab groups, respectively (Table 1). Moreover, 405 patients (placebo: 200/201 [99.5%]; mepolizumab: 205/206 [99.5%]) had a loss of smell VAS score >7–10, indicative of anosmia or severe hyposmia (Table 1).

Owing to operational limitations, only participating sites in the UK, US and Canada used the UPSIT tool for patient assessments; thus, only patients in those countries had baseline UPSIT scores available, equating to approximately one quarter of the ITT population (n=108). These patients had an impaired ability to identify smells at baseline, as indicated by mean (SD) UPSIT

Table 2. Median change from baseline in loss of smell VAS score at Weeks 49–52, by number of OCS courses received during the study.

	Median (IQR; Q1,Q3) change from baseline to Weeks 49–52 in loss of smell VAS score	
	Placebo (N=201)	Mepolizumab (N=206)
Courses of OCS required during the study period		
0	n=127 −0.04 (−3.02, 0.00)	n=154 −1.45 (−6.74, 0.00)
1	n=43 0.00 (−0.04, 0.01)	n=32 0.00 (−1.95, 0.00)
2	n=18 0.00 (−0.17, 0.00)	n=17 −0.07 (−1.74, 0.00)
≥3	n=13 0.00 (−0.14, 0.00)	n=3 −3.49(−5.44, 0.45)

IQR, interquartile range; OCS, oral corticosteroid; VAS, visual analogue scale.

scores of 13.4 (7.45) and 13.0 (6.81) in the placebo and mepolizumab groups, respectively (Table 1). Most patients (placebo: 43/54 [80%]; mepolizumab: 46/54 [85%]) with baseline UPSIT data had UPSIT-defined anosmia (UPSIT scores <19) (Table 1). These patients had slightly poorer mean baseline loss of smell VAS scores than those without UPSIT-defined anosmia (Table 1).

Of the 22 items in the SNOT questionnaire, decreased sense of smell/taste (item 12) had the highest proportion of patients who rated it as 'problem as bad as it could be' at baseline (placebo: 159/201 [80%]; mepolizumab: 159/206 [78%]; Table 1). Mean (SD) baseline SNOT-22 sense of smell/taste item scores were 4.8 (0.50) and 4.7 (0.78) out of 5 in the mepolizumab and placebo groups, respectively, demonstrating an impaired sense of smell and/or taste among the study population (Table 1).

Changes from baseline to Week 52 in olfactory function

Loss of smell VAS score

As described previously, the change from baseline in loss of smell VAS score during Weeks 49–52 in the ITT population was significantly greater with mepolizumab than with placebo (adjusted treatment difference in medians [95% confidence interval (CI)]: −0.37 [−0.65, −0.08]; p=0.020) [19]. Patients with fewer previous surgeries (reported previously) [19] and a shorter time since their last sinus surgery experienced the largest improvements in loss of smell VAS score with mepolizumab versus placebo (Figure 1). Patients experienced more noticeable improvements with mepolizumab versus placebo, irrespective of their baseline blood eosinophil count (Figure 1). With regards to loss of smell improvements by baseline disease severity, mepolizumab-treated patients with a baseline SNOT-22 total score ≤50 had numerically larger improvements in loss of smell VAS score than those with a baseline SNOT-22 score >50 (Figure 2). Patients receiving placebo did not experience improvements in their loss of smell VAS score, irrespective of baseline SNOT-22 subgroup (Figure 2). Baseline median loss of smell VAS scores were similar regardless of baseline SNOT-22 (Figure 2). With regards to OCS use, patients who received no or ≥3 courses of OCS during the study appeared to experience the largest improvements from baseline to Weeks 49–52 in loss of smell VAS score with mepolizumab versus placebo (Table 2). However, the number of patients in the ≥3 courses subgroup was low (n=16).

UPSIT score

As described previously, changes from baseline to Week 52 in UPSIT score were not statistically significant between mepolizumab and placebo treatment groups (adjusted difference in medians [95% CI] 0.40 [–1.49, 2.28]; p=0.30) [19]. The mean (SD) change from baseline in UPSIT score at Week 52 was 0.4 (8.6) with placebo and 1.7 (10.8) with mepolizumab; mean (SD) scores over time are shown in Figure 3A. Of the 54 patients in the mepolizumab group who had UPSIT scores at baseline, 9 (17%) had no anosmia by Week 52; in the placebo group this was 6 out of 54 (11%) patients, although this difference was not statistically significant: 6% (95% CI: -7% to 19%, p=0.40) (Figure 3B).

SNOT-22 sense of smell/taste item score

Significantly larger improvements in the SNOT-22 sense of smell/taste item score from baseline to study end were observed with mepolizumab versus placebo (Figure 4).

Clinical characteristics of patients with and without olfactory improvements during SYNAPSE

Overall, 113 patients were identified as loss of smell VAS responders, indicated by a ≥3-point improvement in loss of smell VAS score between baseline and Weeks 49–52 (Supplementary Table 1). A higher proportion of patients in the mepolizumab group (74/206 [36%]) than in the placebo group (39/201 [19%]) were identified as loss of smell VAS responders (odds ratio [95% CI]: 2.33 [1.48, 3.68]; p<0.001). Mepolizumab-treated patients who were identified as being loss of smell VAS responders had suffered with CRSwNP for less time than those identified as being nonresponders (mean [SD] duration of NP, 10.2 [7.07] vs 12.0 [9.20] years; Supplementary Table 1). A lower proportion of responders had undergone ≥3 previous sinus surgeries compared with nonresponders (17% vs 36%; Supplementary Table 1). Although limited, data from patients without UPSIT-defined anosmia at Week 52 (n=26) support the findings in VAS responders/nonresponders; these patients generally had slightly less severe baseline disease than those with UPSIT-defined anosmia at Week 52 (n=82; Supplementary Table 2).

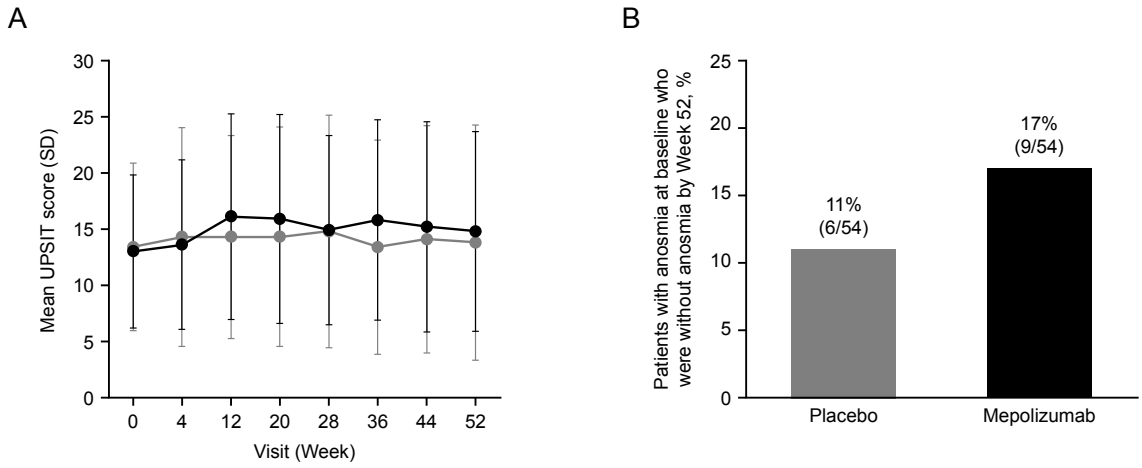

Figure 3. UPSIT scores: A) mean (SD) by study visit and B) proportion of patients who had UPSIT-defined anosmia* at baseline who were without anosmia† by Week 52 ±. Performed at sites in the UK, USA and Canada only. *Defined as UPSIT score <19; † defined as UPSIT score ≥19; ± difference in percent between mepolizumab and placebo at week 52: 6% (95% CI: -7% to 19%, p=0.40). SD, standard deviation; UPSIT, University of Pennsylvania Smell Identification Test.

Discussion

Key results

The primary analysis of the SYNAPSE study showed improved sinonasal symptoms, a reduced need for repeat sinus surgery, and modest improvements in sense of smell with mepolizumab versus placebo among patients with severe CRSwNP [19]. The current analyses characterised sense of smell impairment in recurrent severe CRSwNP, according to several different measures, and provided further information on the impact of mepolizumab versus placebo on improving loss of smell in this patient population. Baseline loss of smell VAS scores demonstrated that patients had a substantially impaired sense of smell pre-treatment, with >99% reporting scores >7–10, indicative of anosmia or severe hyposmia. Moreover, patients had a mean baseline SNOT-22 sense of smell/taste item score of 3.8 (item range 0–5, with higher scores indicating greater symptom severity). Although only around one-quarter of the SYNAPSE population had available UPSIT data, scores further demonstrated an impaired ability to identify smells. The mean baseline UPSIT score was 13.2 (item range 0–40, with scores <19 indicating anosmia) and 80–85% of patients had UPSIT-defined anosmia. Loss of smell VAS scores at baseline were slightly higher among patients with UPSIT-defined anosmia compared with those without anosmia, indicating a possible association between the loss of smell VAS and UPSIT tools. When completing the SNOT-22 questionnaire at baseline, a large proportion of patients (approximately 80%) considered the 'decreased sense of smell/taste' SNOT-22 item 'as bad as it could be', implicating loss of smell as a particularly bothersome symptom of CRSwNP.

The previously reported modest improvements in sense of smell with mepolizumab versus placebo demonstrated by loss of smell VAS scores at Weeks 49–52 [19] appeared to be slightly more pronounced in patients with less severe disease (e.g. fewer previous surgeries, and a shorter time since last sinus surgery). While the overall treatment difference of -0.37 points was below the 3-point threshold for loss of smell VAS that is proposed as being clinically relevant, patients who received mepolizumab were significantly more likely to be classed as a loss of smell VAS responder (i.e., those with a ≥3-point improvement between baseline and Weeks 49–52) than those receiving placebo. Interestingly, loss of smell VAS responders had a shorter duration of NP and fewer sinus surgeries than those identified as nonresponders. Analyses on SNOT-22 sense of smell/taste item score provide supporting evidence for olfactory improvements seen with mepolizumab versus placebo. However, these post hoc analyses should be interpreted with caution due to small patient numbers. Clinically relevant improvements in UPSIT score were not observed; although, very few SYNAPSE patients had UPSIT data available and SYNAPSE was not designed to detect treatment differences in UPSIT. Consequently, results should be interpreted with caution, and additional studies with larger patient numbers would therefore be important to further investigate changes in UPSIT score with mepolizumab treatment.

Interpretation and clinical relevance

Loss of smell is increasingly recognised as a particularly problematic symptom for patients with CRSwNP, being associated with impaired psychological health and reduced HRQoL [11, 21-23]. Reducing symptoms and their impact on HRQoL is one of the goals of CRSwNP treatments [13], and several studies have demonstrated improvements in loss of smell with biologic treatment among patients with CRSwNP. Phase III trials have demonstrated that the IL-4/13 inhibitor dupilumab and the immunoglobulin E inhi-

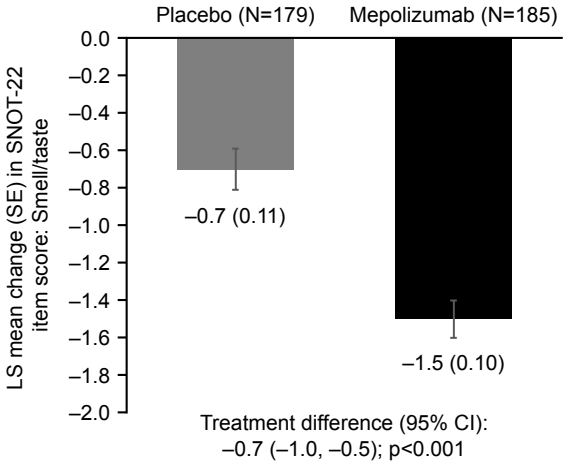

Figure 4. Improvements from baseline in SNOT-22 sense of smell/taste item scores at Week 52. N represents number of patients with analysable data at Week 52. CI, confidence interval; LS, least squares; SNOT-22, SinoNasal Outcomes Test-22; SE, standard error.

bitor omalizumab significantly improve sense of smell according to several patient-reported outcomes [24-26]. Conversely, a Phase III study of the IL-5 α-receptor inhibitor benralizumab found no notable change versus placebo in patients' ability to identify odours, as measured by UPSIT [27]. Some of the findings in the current study differ from those observed in patients receiving dupilumab during the SINUS-24 and SINUS-52 studies, which showed similar loss of smell improvements regardless of surgery history, OCS use, or HRQoL [24]. However, it should be noted that the patient populations recruited in SYNAPSE and the SINUS studies differ substantially [28]. For example, patients in SYNAPSE had a greater surgery history than those in SINUS [19, 29]. Given that surgery is generally performed in patients who do not respond to SoC treatment [13], this may suggest that there were more patients with severe and treatment-refractory disease in SYNAPSE than in the SINUS studies. As such, outcomes from the two studies should not be directly compared without consideration of differing disease severity in the patient populations. Similar to previous assessments of total NP score in the primary analysis of SYNAPSE [19], there was no clear relationship between baseline blood eosinophil count and improvements in loss of smell VAS score in the current analysis. Conversely, a recent exploratory analysis of the SYNAPSE study associated higher baseline blood eosinophil counts with a trend for improved treatment response, as indicated by a decreased risk of surgery and SCS use (although other included endpoints did not show this trend) [30]. This highlights that while blood eosinophil count is a sensitive biomarker for response to mepolizumab in patients with asthma [31, 32], the same effect has not been clearly established in CRSwNP and further investigation is needed.

Olfactory dysfunction in CRSwNP is multifactorial and related to the duration and severity of disease [10]; thus, treatment outcomes may vary. In the current study, the number of prior sinus surgeries was lower and disease duration was shorter in patients who achieved a ≥3-point improvement in loss of smell VAS. The duration of CRS disease has previously been shown to affect improvements in sense of smell following conservative SoC treatment, with patients with CRS ≤2 years demonstrating significantly greater improvements in smell than those with CRS ≥2 years [33]. The authors of that study speculated that treatment before olfactory sensory neuron death and associated remodelling could be key [33]. Indeed, in patients who have a shorter duration of NP, there has been less time for the mechanical obstruction, inflammation, and remodelling of the respiratory and olfactory mucosa. Moreover, eosinophil-secreted factors including Charcot-Leyden crystals, eosinophilic extracellular traps, and eosinophil-derived neurotoxin, which likely accumulate with chronic eosinophilic inflammation, may be associated with olfactory dysfunction [34-37]. Loss of smell has also been significantly associated with a type 2 inflammatory endotype in patients with CRS [2], and an association between multiple endoscopic surgeries and reduced sense of smell has also previously been observed [38, 39]. Surgery can improve olfaction in patients with CSRwNP through surgical removal of mechanical obstruction, removal of inflammatory tissue and opening the sinus ostia [40, 41]. However, damage can occur during surgery, and further reduction in systemic inflammation and blood eosinophilia through non-surgical interventions may be beneficial [40]. Indeed, higher blood eosinophilia, longer course of disease, lower Lund-Mackay scores and peripheral distribution of lesions have been shown to lead to poorer olfactory outcomes following surgery [40]. Additionally, nasal polyp and symptom recurrence is common following surgery, particularly in patients with severe disease and/or type 2 inflammation [41]. In a study by Alobid et al., in patients treated with combined oral and intranasal corticosteroids, smell loss severity correlated with nasal congestion but not mucosal inflammation [42]. Together, these findings suggest that early and systemic intervention may be important to provide the best olfactory response.

Limitations

This analysis has a number of limitations, most notably the post hoc nature of many of the analyses. In addition, the number of patients with available UPSIT data was small because the tool was only available for use in three of the countries participating in the trial, which limits the interpretation of mepolizumab's effect on patients' ability to detect odours. As such, comparison of UPSIT responder and nonresponder subgroups should be interpreted with caution. The measures used to assess sense of smell are subjective, which may introduce variability. Additionally, evidence in patients with CRS suggests that, of the 'Sniffin' Sticks' nasal chemosensory performance test components, odour discrimination may best reflect changes in olfactory function [33];

therefore, as odour discrimination and threshold testing were not used here, as they are infrequently performed by clinicians, this may be considered a study limitation. Nonetheless, these data from the SYNAPSE further demonstrate a beneficial impact of mepolizumab on sense of smell in patients with CRSwNP, in addition to further characterising those patients whose olfaction improved with mepolizumab.

Conclusions

In this analysis of data from the SYNAPSE study, in which patients had substantial loss of smell at baseline, mepolizumab was associated with larger improvements from baseline in patients' perception of smell, as measured by loss of smell VAS score and SNOT-22 sense of smell/taste item score compared with placebo. Mepolizumab-treated patients with the largest improvements in their loss of smell VAS scores had fewer prior endoscopic surgeries and shorter disease duration, suggesting greater clinical benefit may be achieved in these patient populations. Given the significant impact of loss of smell on quality of life among patients with severe CRSwNP, these data should be considered when making treatment decisions.

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Authorship contribution

MW, JKH, and WF contributed to the acquisition of study data, data analysis, and interpretation. ARS, BM, and RHC contributed to the conception or design of the study, data analysis, and interpretation. JM, VL, and SGS contributed to the data analysis and interpretation. All authors developed, revised, and critically reviewed the manuscript, and provided final approval of the version submitted for publication. All authors participated in the development of the manuscript and had access to the study data.

Conflict of interest

JM has received research grants from AstraZeneca, GSK, Viatris (Mylan-Meda Pharmaceuticals), Regeneron Pharmaceuticals Inc., Sanofi Genzyme and Uriach Group, has received consulting fees from Sanofi and Uriach group and has participated in advisory boards or speakers' bureaus for AstraZeneca, GSK, Menarini, Mitsubishi-Tanabe Pharma, MSD, Viatris (Mylan-Meda Pharmaceuticals), Novartis, Proctor & Gamble, Regeneron Pharmaceuticals Inc., Sanofi-Genzyme, UCB Pharma, and Uriach Group. VL has received advisory board and lecture fees from Abbot, Novartis, GSK and Sanofi and is a member of the Chrinosor CRS Registry Steering Group and a trustee of the NASE Foundation. MW has received personal fees from ALK-Abelló, AstraZeneca, Genzyme, GSK, Allergie, Infectopharm, LETI Pharma, Med update, Novartis, Regeneron, Sanofi and, Stallergenes and is a member of the executive committee (treasurer), Head of the Section Otorhinolaryngology of the Deutsche Gesellschaft für Allergie und klinische Immunologie (German Society of Allergology and Clinical Immunology); MW's institution has received payments from ALK-Abelló, AstraZeneca, GSK, Novartis, Regeneron, Sanofi-Aventis and Takeda. JKH has received consultancy fees from Sanofi Genzyme, Regeneron, Genentech, Novartis, AstraZeneca, GSK, and Gossamer Bio. ARS, SGS, BM, and RHC are employees of GSK and own stocks/shares. WF has received research grants from GSK, Sanofi and Novartis, consulting fees from Sanofi and GSK, honoraria from GSK, Sanofi and Novartis, clinical trial funding from Sanofi, Mylan, ALK, Allergy Therapeutics, Novartis, Chordate, and GSK, personal fees from Sanofi and GSK and is secretary general of ERS and editor-in-chief of *Rhinology*.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Supplementary section 1

Details of the visual analogue scale.

When using the visual analogue scale (VAS) tool, patients quantify the severity of their symptoms on an electronic device which represents 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).

Supplementary Table 1. Baseline demographics and characteristics in loss of smell VAS score responders and nonresponders.

	Loss of smell VAS responders* (N=113)			Loss of smell VAS nonresponders † (N=294)		
	Placebo (N=39)	Mepolizumab (N=74)	Total (N=113)	Placebo (N=162)	Mepolizumab (N=132)	Total (N=294)
Female, n (%)	11 (28)	25 (34)	36 (32)	65 (40)	42 (32)	107 (36)
Age, years, mean (SD)	48.6 (11.86)	48.9 (13.39)	48.8 (12.83)	48.9 (12.64)	48.5 (13.69)	48.7 (13.1)
BMI, kg/m^2, mean (SD)	28.0 (5.12)	27.3 (4.50)	27.5 (4.71)	28.2 (5.55)	28.6 (5.61)	28.4 (5.57)
Duration of NP, years, mean (SD)	11.0 (7.74)	10.2 (7.07)	10.5 (7.3)	11.6 (8.42)	12.0 (9.20)	11.8 (8.76)
Total endoscopic NP score, mean (SD)	5.1 (1.49)	5.4 (1.07)	5.3 (1.23)	5.7 (1.37)	5.4 (1.22)	5.5 (1.31)
Overall VAS score, mean (SD)	8.9 (0.76)	9.1 (0.74)	9.0 (0.7)	9.1 (0.71)	9.0 (0.79)	9.1 (0.75)
Nasal obstruction VAS score, mean (SD)	8.9 (0.87)	8.9 (0.84)	8.9 (0.85)	9.1 (0.82)	8.9 (0.83)	9.01 (0.82)
Nasal symptoms composite VAS score, mean (SD)	9.0 (0.71)	9.0 (0.83)	9.0 (0.79)	9.0 (0.86)	9.0 (0.79)	9.0 (0.83)
Loss of smell VAS score, mean (SD)	9.4 (0.70)	9.7 (0.55)	9.6 (0.61)	9.7 (0.55)	9.6 (0.96)	9.7 (0.76)
UPSIT score, mean (SD) ‡	21.5 (10.01)	14.5 (6.91)	17.1 (8.71)	12.0 (6.02)	12.6 (6.80)	12.3 (6.36)
SNOT-22 total score, mean (SD)	60.0 (17.75)	60.3 (17.87)	60.2 (17.75)	65.5 (19.24)	65.6 (17.28)	65.5 (18.35)
Time since most recent NP surgery, years, mean (SD)	3.7 (2.73)	4.2 (2.57)	4.0 (2.62)	3.9 (2.68)	4.2 (2.75)	4.0 (2.71)
Number of surgeries for NP in the past 10 years, n (%)						
0	0	0	0	0	0	0
1	19 (49)	46 (62)	65 (58)	62 (38)	62 (47)	124 (42)
2	13 (33)	16 (22)	29 (26)	34 (21)	31 (23)	65 (22)
≥3	7 (18)	12 (16)	19 (17)	66 (41)	39 (30)	105 (36)
Number of OCS courses for NP in the past 12 months, n (%)						
0	24 (62)	37 (50)	61 (54)	86 (53)	63 (48)	149 (51)
1	9 (23)	22 (30)	31 (27)	38 (23)	42 (32)	80 (27)
2	3 (8)	7 (9)	10 (9)	15 (9)	10 (8)	25 (9)
>2	3 (8)	8 (11)	11 (10)	23 (14)	17 (13)	40 (14)
Comorbid asthma, n (%)	24 (62)	49 (66)	73 (65)	125 (77)	91 (69)	216 (73)
Comorbid AERD, n (%)	6 (15)	16 (22)	22 (19)	57 (35)	29 (22)	86 (29)
Blood eosinophil count, cells/μL, geometric mean (SD logs)	320 (0.782)	350 (0.719)	340 (0.740)	420 (0.766)	410 (0.772)	410 (0.768)

*Patients with ≥3-point improvement from baseline in loss of smell VAS score at Weeks 49–52; † patients with <3-point improvement from baseline in loss of smell VAS score at Weeks 49–52; ‡ in the subset of patients for whom UPSIT data were available (loss of smell VAS responders: placebo n=8, mepolizumab n=13; loss of smell VAS nonresponders: placebo n=46, mepolizumab n=41). AERD, aspirin-exacerbated respiratory disease; BMI, body mass index; NP, nasal polyps; OCS, oral corticosteroid; SD, standard deviation; SNOT-22, Sino-Nasal Outcomes Test-22; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analogue scale.

Supplementary Table 2. Baseline demographics and characteristics among patients with UPSIT-defined anosmia and hyposmia/normosmia at Week 52.

	Patients without UPSIT-defined hyposmia/normosmia* at Week 52 (N=26)			Patients with UPSIT-defined anosmia † at Week 52 (N=82)		
	Placebo (n=14)	Mepolizumab (n=12)	Total (n=26)	Placebo (n=40)	Mepolizumab (n=42)	Total (n=82)
Female, n (%)	3 (21)	3 (25)	6 (23)	17 (43)	10 (24)	27 (33)
Age, years, mean (SD)	51.0 (12.85)	52.2 (11.72)	51.5 (12.11)	46.9 (12.88)	47.1 (15.49)	47.0 (14.19)
BMI, kg/m^2, mean (SD)	29.2 (6.32)	28.8 (4.50)	29.05 (5.46)	29.7 (6.78)	29.5 (5.78)	29.6 (6.25)
Duration of NP, years, mean (SD)	13.0 (6.81)	13.3 (8.98)	13.1 (7.72)	11.0 (7.87)	13.0 (9.29)	12.0 (8.63)
Total endoscopic NP score, mean (SD)	4.7 (1.59)	5.4 (1.00)	5.0 (1.37)	6.1 (1.34)	5.5 (1.33)	5.8 (1.37)
Overall VAS score, mean (SD)	8.7 (0.76)	8.6 (0.92)	8.7 (0.82)	9.2 (0.76)	9.0 (0.89)	9.1 (0.83)
Nasal obstruction VAS score, mean (SD)	8.6 (0.88)	8.5 (1.09)	8.6 (0.96)	9.1 (0.81)	9.0 (0.88)	9.1 (0.84)
Nasal symptoms composite VAS score, mean (SD)	8.7 (0.87)	8.5 (0.90)	8.6 (0.87)	9.0 (0.89)	9.0 (0.77)	9.0 (0.83)
Loss of smell VAS score, mean (SD)	9.2 (1.04)	9.4 (0.98)	9.3 (1.0)	9.9 (0.28)	9.7 (0.57)	9.8 (0.45)
UPSIT score, mean (SD)	20.5 (9.84)	13.7 (7.46)	17.3 (9.32)	11.0 (4.36)	12.9 (6.69)	11.9 (5.72)
SNOT-22 total score, mean (SD)	54.4 (14.16)	61.7 (19.69)	57.7 (16.99)	68.4 (23.06)	67.4 (18.60)	67.9 (20.71)
Time since most recent NP surgery, years, mean (SD)	4.3 (2.83)	3.5 (2.35)	3.9 (2.60)	2.9 (2.07)	4.0 (2.91)	3.5 (2.58)
Number of surgeries for NP in the past 10 years, n (%)						
0	0	0	0	0	0	0
1	5 (36)	5 (42)	10 (38)	16 (40)	18 (43)	23 (41)
2	3 (21)	3 (25)	6 (23)	6 (15)	12 (29)	18 (22)
≥3	6 (43)	4 (33)	10 (39)	18 (45)	12 (29)	30 (37)
Number of OCS courses for NP in the past 12 months, n (%)						
0	8 (57)	5 (42)	13 (50)	16 (40)	15 (36)	31 (38)
1	2 (14)	3 (25)	5 (19)	10 (25)	14 (33)	24 (29)
2	1 (7)	0	1 (4)	7 (18)	5 (12)	12 (15)
>2	3 (21)	4 (33)	7 (27)	7 (18)	8 (19)	15 (18)
Comorbid asthma, n (%)	9 (64)	10 (83)	19 (73)	35 (88)	34 (81)	69 (84)
Comorbid AERD, n (%)	4 (29)	3 (25)	7 (27)	15 (38)	10 (24)	25 (30)
Blood eosinophil count, cells/µL, geometric mean (SD logs)	450 (0.612)	490 (0.687)	470 (0.636)	500 (0.868)	470 (0.659)	480 (0.764)

*Patients with UPSIT scores ≥19; † patients with UPSIT scores <19. UPSIT was carried out only for patients in Canada, the United Kingdom, and the United States of America. AERD, aspirin-exacerbated respiratory disease; BMI, body mass index; NP, nasal polyps; OCS, oral corticosteroid; SD, standard deviation; SNOT-22, Sino-Nasal Outcomes Test-22; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analogue scale.

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