Mepolizumab Reduces Disease Symptoms for Patients With Chronic Rhinosinusitis With Nasal Polyps: Data From the SYNAPSE Study

Poster No. 402

Tabberer M[1], Trigg A[2], Busse W[3], Lund V[4], Lee JK[5], Bachert C[6], Senior B[7], Buchheit KM[8], Diamant Z[9,10,11], Sousa AR[12], Smith SG[13], Mayer B[14], Yancey SW[13], Chan RH[15]

[1]Respiratory Patient Centered Outcomes, Value Evidence and Outcomes, GSK, GSK House, Brentford, Middlesex, UK; [2]Patient-Centered Outcomes, Adelphi Values, Bollington, Cheshire, UK; [3]Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; [4]Royal National Throat, Nose and Ear Hospital, UCLH, London, UK; [5]Toronto Allergy and Asthma Centre, Evidence Based Medical Educator, Toronto, ON, Canada and University of Kansas Medical Center, Kansas City, KS, USA; [6]Upper Airways Research Laboratory and Department of Oto-Rhino-Laryngology, Ghent University and Ghent University Hospital, Ghent, Belgium and Division of ENT Diseases, CLINTEC, Karolinska Institute, University of Stockholm, Stockholm, Sweden; [7]UNC Otorhinolaryngology/Head and Neck Surgery, Division of Rhinology, Allergy, and Endoscopic Skull Base Surgery and Department of Neurosurgery, University of North Carolina School of Medicine, Chapel Hill, NC, USA; [8]Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, MA, USA; [9]Department of Microbiology Immunology & Transplantation, KU Leuven, Catholic University of Leuven, Leuven, Belgium; [10]Department of Clinical Pharmacy & Pharmacology, UMCG, Groningen, the Netherlands; [11]Respiratory Medicine and Allergology, Skane University, Lund, Sweden; [12]Respiratory Therapy Unit, GSK, GSK House, Brentford, Middlesex, UK; [13]Respiratory Therapeutic Area Unit, GSK, Research Triangle Park, NC, USA; [14]Clinical Statistics, GSK, GSK House, Brentford, Middlesex, UK; [15]Clinical Sciences, GSK R&D, GSK House, Brentford, Middlesex, UK

Introduction

- Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterized by eosinophilic inflammation, driven by type 2 cytokines such as IL-5.[1,2] Clinical manifestations include nasal blockage, facial pain, loss of smell and rhinorrhea.[3,4]
- Determining symptom severity from the patient's perspective is key to assessing treatment efficacy in clinical trials and to providing personalized care in the clinic. The EAACI Position Paper on Rhinosinusitis and NP (EPOS 2020) supports the use of the visual analogue scale (VAS) to assess symptom severity in patients with CRSwNP.[5]
- The Phase III SYNAPSE study assessed the efficacy of 4-weekly add-on mepolizumab 100 mg SC in patients with CRSwNP in need of repeat nasal surgery and measured their daily symptoms.[6] SYNAPSE demonstrated significant improvements from baseline in total endoscopic NP score and Nasal Obstruction VAS score following mepolizumab treatment versus placebo.[6]
- The measurement properties of VAS to assess symptoms were previously evaluated using data from a Phase II study[7] of mepolizumab in patients with CRSwNP; VAS items were subsequently modified for inclusion in the SYNAPSE study to improve clarity and, therefore, patient comprehension and interpretation.
- To explore the measurement properties of these updated VAS, including definitions of response, psychometric analyses were conducted using blinded data from SYNAPSE.[6]
- This poster reports both the findings from these blinded psychometric analyses, which estimated meaningful within-patient change thresholds for patient-reported VAS questions on Nasal Obstruction, Mucus in Throat, Loss of Smell, Facial Pain, Nasal Discharge, and Overall Symptoms VAS and uses these thresholds to report the efficacy of mepolizumab versus placebo on patient-reported symptoms in CRSwNP.

Methods

Study design

GSK ID: 205687/NCT03085797 (SYNAPSE)

Phase III trial

Randomized, double-blind, placebo-controlled

Patients were given placebo or mepolizumab 100 mg SC every 4 weeks for 52 weeks

Patients were also given standard of care: daily MF and saline nasal douching, occasional short courses of high dose OCS, and/or antibiotics when required

Eligibility criteria

- ≥18 years of age
- ≥1 prior[a] surgery[†]
- Need for surgery[‡]
- Bilateral NP diagnosis
- Obstruction VAS score >5
- Non- or former smoker (>6 month)
- No biologic or immunosuppressant treatment
- No concurrent medical condition
- No SCS use <4 weeks prior to screening

Efficacy analysis

Co-primary endpoints[§]
- Change from baseline in total endoscopic NP score at Week 52
- Change from baseline in Nasal Obstruction VAS score during Weeks 49–52

Secondary endpoints
- Change from baseline in Loss of Smell VAS score at Weeks 49–52
- Change from baseline in Overall Symptoms VAS score at Weeks 49–52

Other endpoints
- Change from baseline in Nasal Discharge, Mucus in Throat, and Facial Pain VAS scores at Weeks 49–52

VAS assessments
- Patients completed the six individual VAS daily using an eDiary and a recall period of 24 hours
- Individual VAS were rated on a 0–100 measured scale and transformed to a 0–10 scale for reporting
- Greater scores indicate greater symptom severity

Blinded psychometric analyses (post hoc)
- Post hoc anchor-based analyses were performed for individual VAS scores using data from baseline and Week 52 in the psychometric analysis population, which included all patients from the intent-to-treat population
- Polyserial correlation coefficient calculations were used to assess the relationship between potential anchors and change in VAS score
- Potential anchors included endoscopic NP score, PNIF, Overall VAS, and SNOT-22. Anchors with a coefficient of ≥0.3 were selected
- Selected anchors were used to define patients as minimally improved or stable. Results from these patients are shown in Table 2. CDF and PDF plots split by anchor categories aided comparison of thresholds for meaningful within-patient change

Efficacy assessments
- Efficacy of mepolizumab versus placebo was determined in patients using the estimated thresholds for meaningful within-patient change
- Median change from baseline in individual and Overall Symptoms VAS scores, median change from baseline in Nasal Obstruction VAS scores in patients with and without comorbid asthma, and the effect of prior surgeries on Loss of Smell VAS were assessed at Weeks 49–52

Baseline was defined as the mean VAS score from the last 7 days prior to randomization. [a]Within the last 10 years; [†]defined as any procedure involving instruments with resulting incision and removal of polyp tissue from the nasal cavity; [‡]defined by an overall VAS symptom score >7 and an endoscopic bilateral NP score ≥5 (with a minimum score of 2 per nasal cavity); [§]results published previously.[6]

Results

Baseline demographics

- Of the 407 patients included in the study, 206 received mepolizumab and 201 received placebo. Most (65%) patients were male with a mean (SD) age of 48.8 (13.0) years.
- At baseline, the median VAS scores were similar between groups (**Table 1**).

Table 1. Baseline demographics and characteristics

	Placebo (n=201)	Mepolizumab 100 mg SC (n=206)	Total (n=407)
Age, years, mean (SD)	48.9 (12.5)	48.6 (13.6)	48.8 (13.0)
Sex, n (%)			
Male	125 (62)	139 (67)	264 (65)
Blood eosinophil count, cells/μL, geometric mean (standard logs)	400 (0.775)	390 (0.755)	-
Patients with asthma, n (%)	149 (74)	140 (68)	289 (71)
Prior nasal surgeries*			
1	81 (40)	108 (52)	189 (46)
2	47 (23)	47 (23)	94 (23)
>2	73 (36)	51 (25)	124 (30)
Duration of NP, years, mean (SD)	11.46 (8.27)	11.36 (8.52)	11.41 (8.39)
VAS score†, median (range)			
Nasal Obstruction	9.1 (5.3–10.0)	9.0 (6.5–10.0)	9.1 (5.3–10.0)
Loss of Smell	10.0 (6.7–10.0)	10.0 (0.9–10.0)	10.0 (0.9–10.0)
Overall Symptoms	9.2 (7.2–10.0)	9.1 (7.2–10.0)	9.2 (7.2–10.0)
Nasal Discharge	9.0 (1.4–10.0)	8.9 (1.0–10.0)	-
Mucus in Throat	9.0 (0.5–10.0)	8.9 (0.2–10.0)	-
Facial Pain	8.9 (0.0–10.0)	8.5 (0.0–10.0)	-

*Number of previous surgeries for NP in the past 10 years; †VAS scores were completed daily, reported as 4-weekly means on 0–10 scale. Greater VAS scores indicate greater disease severity.

Psychometric analyses

- Anchors based on the SNOT-22 and Overall Symptoms VAS were sufficiently correlated (r≥0.3) with change in VAS scores and thus suitable for use.
- The mean anchor-based changes from baseline to Week 52 in VAS scores for patients categorized as stable or minimally improved are displayed in **Table 2**. These data, combined with inspection of CDF and PDF plots, informed a meaningful within-patient change threshold of -2.5-points (improvement) for Overall Symptoms, Nasal Discharge, and Facial Pain VAS and a threshold of -3.0-points (improvement) for Nasal Obstruction, Loss of Smell, and Mucus in Throat VAS.

Table 2. Anchor-based change from baseline to Week 52 for individual VAS scores

Anchor	Nasal Obstruction	Loss of Smell	Overall Symptom	Nasal Discharge	Mucus in Throat	Facial Pain
Overall VAS, mean (95% CIs)			-			
Minimal improvement n=49	-3.16 (-3.42, -2.90)	-1.11 (-1.58, -0.65)		-3.25 (-3.65, -2.86)	-3.25 (-3.77, -2.73)	-2.99 (-3.46, -2.52)
Stable n=85	-0.45 (-0.63, -0.26)	-0.33 (-0.50, -0.16)		-0.55 (-0.87, -0.23)	-0.54 (-0.91, -0.16)	-0.49 (-0.88, -0.11)
SNOT-22 Total Score						
Minimal improvement, n=31	-2.80 (-3.70, -1.90)	-1.51 (-2.46, -0.57)	-2.94 (-3.92, -1.97)	-2.58 (-3.51, -1.65)	-2.33 (-3.37, -1.29)	-2.62 (-3.64, -1.59)
Stable, n=38	-1.77 (-2.61, -0.93)	-1.05 (-1.83, -0.27)	-1.84 (-2.69, -0.99)	-1.80 (-2.64, -0.96)	-2.07 (-2.94, -1.20)	-1.58 (-2.50, -0.66)
SNOT-22 Nasal Obstruction		-	-	-	-	-
Minimal improvement, n=86	-4.66, (-5.23, -4.09)					
Stable, n=113	-2.62 (-3.12, -2.13)					
SNOT-22 Loss of Taste or Smell	-		-	-	-	-
Minimal improvement, n=43		-4.35 (-5.24, -3.46)				
Stable, n=187		-1.05 (-1.34, -0.75)				
SNOT-22 Thick Nasal Discharge	-	-	-		-	-
Minimal improvement, n=81				-5.08 (-5.76, -4.39)		
Stable, n=113				-2.75 (-3.27, -2.23)		
SNOT-22 Post-Nasal Discharge	-	-	-	-		-
Minimal improvement, n=75					-4.83 (-5.49, -4.17)	
Stable, n=137					-2.96 (-3.47, -2.44)	
SNOT-22 Facial Pain/Pressure	-	-	-	-	-	
Minimal improvement, n=78						-4.82 (-5.51, -4.14)
Stable, n=130						-2.66 (-3.18, -2.13)

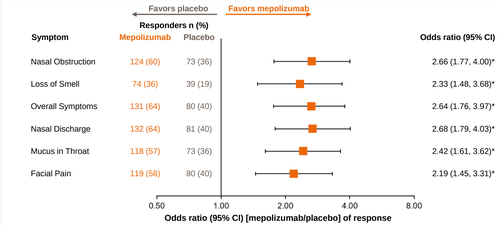
Improvement group definitions: Overall VAS symptom score: Minimal improvement -2≥ change score >-4, stable -2< change score <2; SNOT-22 Total score: Minimal improvement -8.9≥ change score >-17.8, stable -8.9< change score <8.9; SNOT-22 Nasal Obstruction, SNOT-22 Loss of Taste or Smell, SNOT-22 Thick Nasal Discharge, SNOT-22 Facial Pain/Pressure, and SNOT-22 Post-Nasal Discharge: Minimal improvement -2, stable -2< change score <2.

Efficacy assessments

Responder analysis

- Compared with placebo, patients receiving mepolizumab were more likely to demonstrate a meaningful improvement in VAS scores, based on meeting or exceeding the meaningful within-patient change thresholds at Weeks 49–52 (**Figure 1**).

Figure 1. Probability of meaningful within-patient change in VAS score (Weeks 49–52)

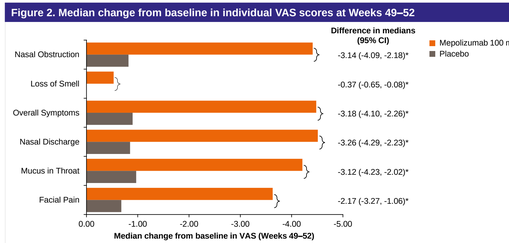


Meaningful within-patient change was indicated by ≥-2.5-point change (improvement) for Overall Symptoms, Nasal Discharge, and Facial Pain VAS scores, and a ≥-3 point change (improvement) for Nasal Obstruction, Loss of Smell, and Mucus in Throat VAS scores. The analysis was performed using a logistic regression model with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count. *P<0.001.

Mepolizumab improved symptoms in patients with CRSwNP versus placebo

- Mepolizumab treatment was associated with a significantly greater change from baseline in individual VAS scores compared with placebo at Weeks 49–52 (*P*<0.001) (**Figure 2**).
- While some (n=74/206, 36%) patients receiving mepolizumab did exceed the meaningful within-patient change threshold in Loss of Smell VAS compared with baseline, this was the only VAS for which the median change from baseline did not exceed the threshold.

Figure 2. Median change from baseline in individual VAS scores at Weeks 49–52



The analysis was performed using quantile regression, with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count. For individual VAS scores, the analysis presented treatment effect as difference in medians to reduce the influence of extremes in the data. *P<0.001.

Conclusions

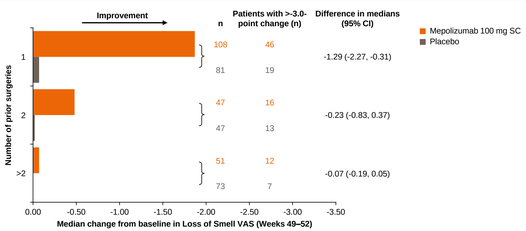
- Psychometric analyses indicate a meaningful within-patient change threshold of -2.5-points for Overall Symptoms, Nasal Discharge, and Facial Pain VAS and a threshold of -3.0-points for Nasal Obstruction, Loss of Smell, and Mucus in Throat VAS.
- The odds of patients achieving a response above the meaningful within-patient change threshold in each VAS score was significantly greater for patients receiving mepolizumab than patients receiving placebo.
- Clinically and statistically significant improvements in symptoms were demonstrated with mepolizumab 100 mg SC compared with placebo.
- The efficacy of mepolizumab on loss of smell was greatest in patients who had undergone 1 prior surgery versus patients who had undergone multiple prior surgeries. This may be related to the increased scarring and nerve damage associated with repeat surgeries, which limits any potential for recovery of sense of smell. This can impact taste and substantially affect health-related quality of life.

- In both groups, the median change from baseline in Nasal Obstruction VAS score was similar in patients with and without concurrent asthma (mepolizumab: concurrent asthma, -4.27; without asthma, -4.69; placebo: concurrent asthma, -0.75; without asthma, -1.40).

The effect of prior surgeries on Loss of Smell VAS scores

- Patients who had undergone ≥2 surgeries prior to treatment with mepolizumab showed less improvement in median change from baseline in Loss of Smell VAS compared with patients who had undergone 1 surgery prior to mepolizumab treatment (**Figure 3**).

Figure 3. Median change from baseline in Loss of Smell VAS score at Weeks 49–52 by number of prior surgeries



The analysis was performed using quantile regression, with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count.

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Abbreviations

CDF, cumulative distribution function; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; EAACI, European Academy of Allergy and Clinical Immunology; EPOS, EAACI Position Paper on Rhinosinusitis and NP; IL, interleukin; MF, mometasone furoate; NP, nasal polyps; OCS, oral corticosteroids; PDF, probability distribution function; PNIF, peak nasal inspiratory flow; SC, subcutaneous; SCS, systemic corticosteroids; SD, standard deviation; VAS, visual analog scale.

Disclosures

- This study and post hoc analysis were funded by GlaxoSmithKline (GSK ID: 205687; NCT03085797).
- On behalf of all authors, an audio recording of this poster was prepared by Maggie Tabberer, who did not receive any payment for this recording.
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- Editorial support (in the form of writing assistance, including, assembling tables and figures, collating authors' comments, grammatical editing and referencing) was provided by Laura Murch, PhD, Fishawack Indicia Ltd, UK, part of Fishawack Health, and was funded by GSK.

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Prepared for the American Academy of Allergy Asthma & Immunology Annual Meeting 2021