SYNAPSE
Clinical Trial Brief

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SYNAPSE Phase 3 Pivotal Trial Overview

SYNAPSE was a controlled trial designed to investigate the efficacy and safety of mepolizumab compared with placebo in adult patients with recurrent, refractory, severe, bilateral CRSwNP who were eligible for repeat surgery.[a] A summary of study methods and select efficacy and safety results are presented below.

Study Methods

Key Inclusion and Exclusion Criteria

Key inclusion criteria

- ≥18 years of age
- Recurrent, refractory, severe, bilateral nasal polyp symptoms, defined as:
  - Bilateral endoscopic NPS ≥5
  - Nasal obstruction VAS symptom score of >5 (maximum 10)
- ≥1 surgery in previous 10 years[b]
- Current need for surgery
  - Defined as overall VAS symptom score >7 and NPS ≥5 [maximum 8] with a minimum score of 2 in each nasal cavity (despite SOC treatment)
- Stable intranasal corticosteroids for ≥8 weeks prior to screening
- ≥2 different symptoms for ≥12 weeks before screening (eg, nasal blockage, obstruction, and congestion or nasal discharge [anterior or posterior nasal drip]) with ≥1 of the following symptoms: nasal discharge, facial pain or pressure, reduction or loss of smell

Key exclusion criteria

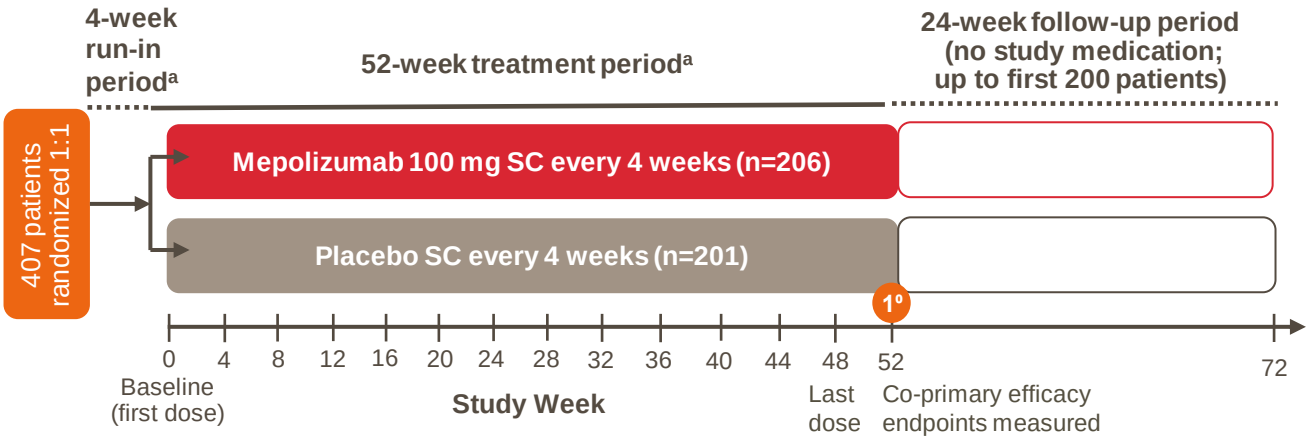
- Certain comorbid disorders and other medical conditions, such as EGPA, cystic fibrosis, antrochoanal polyps,[c] and nasal septal deviation blocking 1 nostril
- Acute sinusitis or upper respiratory tract infection within 2 weeks prior to screening
- Rhinitis medicamentosa (rebound or chemical-induced rhinitis)
- Asthma exacerbation requiring hospital admission within 4 weeks of screening
- Any intranasal and/or sinus surgery within 6 months prior to screening (including polypectomy, balloon dilatation, stent insertion)
- Contraindication for nasal surgery
- Biologic or immunosuppressive treatment within 5 half-lives or omalizumab within 130 days of screening
- Known, pre-existing parasitic infection within 6 months of screening
- Smoker currently or in prior 6 months

[a]Han et al. *Lancet Respir Med.* April 16, 2021. Published online: https://doi.org/10.1016/S2213-2600(21)00097-7.
[b]Any incision of the paranasal sinuses and removal of polyp tissue from the nasal cavity (polypectomy) and the sinuses.
[c]A solitary nasal polyp found near the posterior wall of the maxillary sinus.

CRSwNP, chronic rhinosinusitis with nasal polyps
EGPA, eosinophilic granulomatosis with polyangiitis
HQ, headquarters
NPS, Nasal Polyp Score
SOC, standard of care
VAS, Visual Analogue Scale

Study Design

- Randomized, placebo-controlled, double-blind, parallel-group, multicenter, phase 3 study
- Patients received mepolizumab 100 mg or placebo SC once every 4 weeks (using prefilled syringe) for 52 weeks while continuing standard-of-care treatment, including:
  - Mometasone furoate nasal spray (MFNS; maximum of 2 doses of 50 µg into each nostril twice daily)
  - Saline nasal irrigations
  - Courses of SCS or antibiotics, or both, as required



[a]MFNS administered during run-in period and double-blind periods.

Endpoints

Co-primary endpoints

Change from baseline in **total endoscopic NPS** at Week 52 (nasal polyp size)

Change from baseline in **nasal obstruction VAS score** during Weeks 49 to 52 (nasal polyp symptoms)

Secondary endpoints[b]

Key secondary endpoint: Time to first nasal surgery (nasal polypectomy) up to Week 52[c]

Additional secondary endpoints

- Change from baseline in overall, composite, and individual loss of smell VAS symptom scores during Weeks 49 to 52 (nasal polyp symptoms)
- Change from baseline in SNOT-22 total score at Week 52 (health-related quality of life [HRQoL])
- Proportion of patients requiring systemic corticosteroids (SCS) up to Week 52

[b]Multiplicity controlled through statistical testing of secondary endpoints following a predefined hierarchy.
[c]Defined as any procedure involving instruments resulting in incision and removal of tissue in the nasal cavity and sinuses.

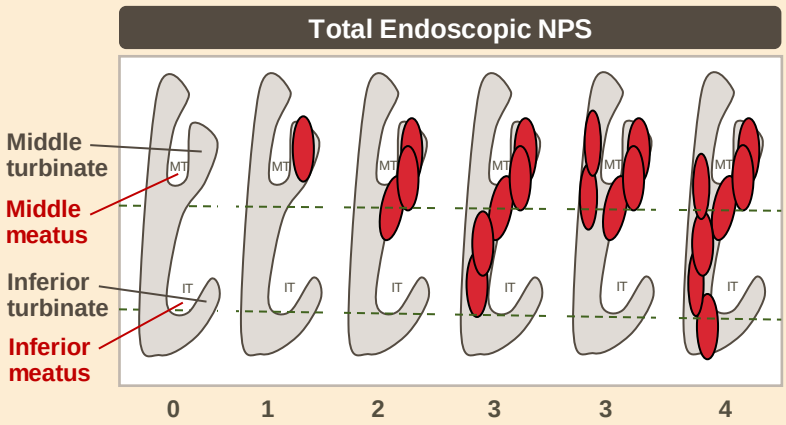
NPS, Nasal Polyp Score
SC, subcutaneous
SCS, systemic corticosteroids
SNOT-22, Sino-Nasal Outcome Test-22
VAS, Visual Analogue Scale

Definitions of Key Endpoint Measures

Total Endoscopic NPS

- A physician-reported tool for grading the severity of nasal polyps based on nasal endoscopy findings
- Each nostril was assessed for polyps and graded from 0 to 4 at each study visit
- Scores were centrally read by independent, blinded assessors to remove bias

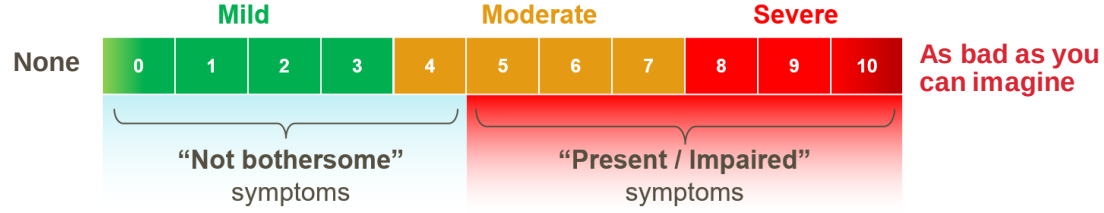
Polyp Score	Polyp Size
0	No polyps
1	Small polyps in middle meatus, not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the border of the middle turbinate
3	Large polyps reaching the lower border of inferior turbinate or polyps medial to the middle turbinate
4	Large polyps causing complete obstruction of the inferior meatus (nasal cavity)



Total endoscopic NPS =
Sum of the left and right nostril scores (0–8)

Visual Analogue Scale (VAS) Symptom Score

- VAS is a tool used to represent subjective, patient-reported severity of symptoms associated with CRSwNP from mild to severe (0-10)
  - Patients indicated the severity of 5 nasal polyp symptoms (nasal obstruction, nasal discharge, throat mucus, loss of smell, and facial pain) on a VAS each day
  - A composite VAS score combined scores for nasal obstruction, nasal discharge, throat mucus, and loss of smell
  - Patients also completed an overall VAS symptoms score each day



SNOT-22 Total Score

- A 22-item, disease-specific, health-related quality of life questionnaire completed by patients that assesses symptoms and symptom impact associated with CRSwNP
  - Each item is scored from 0 (no problem) to 5 (problem as bad as it can be), with total score ranging from 0 to 110 (higher scores generally indicating more severe disease)
- Participants were asked to rate the severity of their condition on each of the 22 items over the previous 2 weeks using a 6-point rating scale of 0-5 at each study visit
- Minimal clinically important difference was 8.9 points

CRSwNP, chronic rhinosinusitis with nasal polyps
NPS, Nasal Polyp Score
SNOT-22, Sino-Nasal Outcome Test-22

Select Baseline Patient Characteristics[a]

Demographics (N=407)

35%
Female

93%
White

Age
49 years

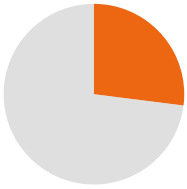
Baseline disease characteristics (N=407)

11.4 years
Duration of nasal polyp disease

Blood eosinophil count[b]
390 cells/µL

48%
Patients with ≥1 SCS course in past year

71%
Patients with comorbid asthma[c]



27%
Patients with comorbid AERD

100%
Patients with ≥1 previous nasal surgery

30%
Patients with ≥3 previous nasal surgeries

5.5 ± 1.29
Total NPS score (maximum score, 8)

9.1 ± 0.74
Overall VAS symptoms score (maximum score, 10)

9.0 ± 0.83
Nasal obstruction VAS score (maximum score, 10)

9.0 ± 0.82
Composite symptoms VAS score (maximum score, 10)

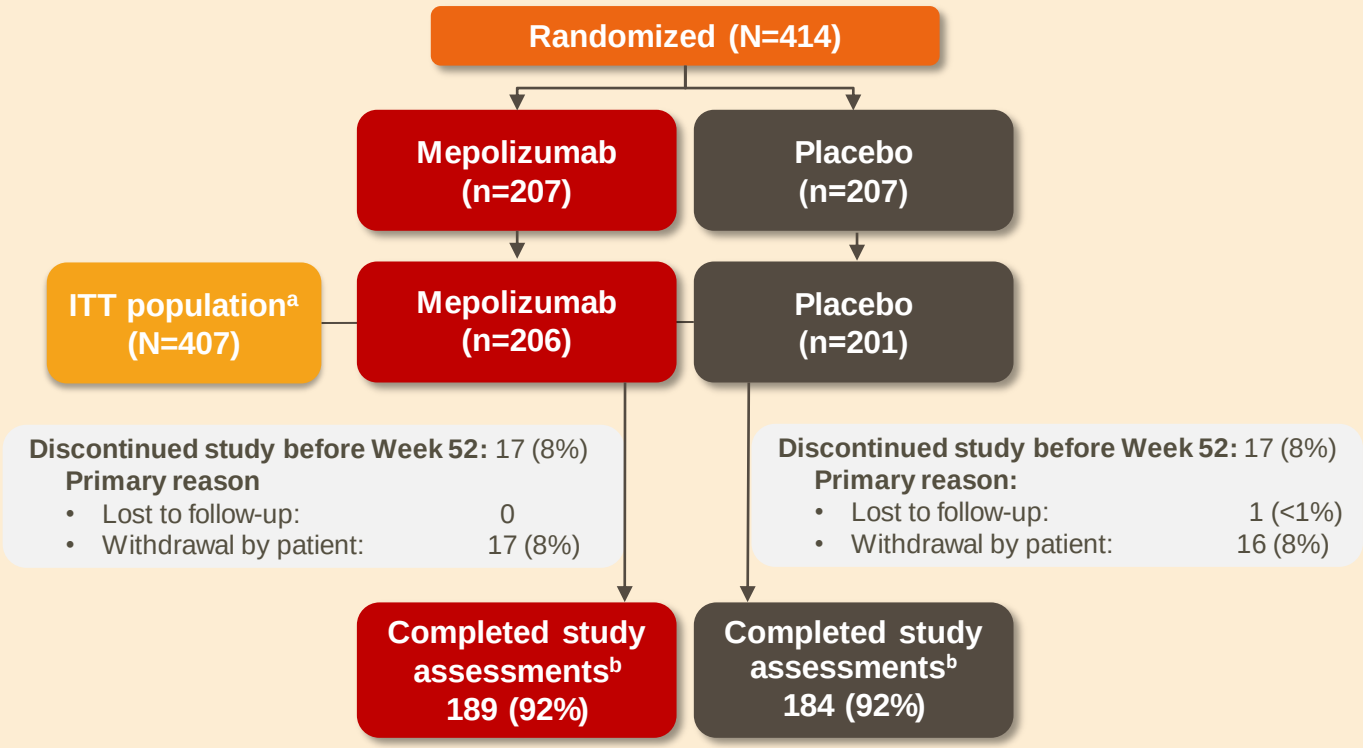
64.1 ± 18.32
SNOT-22 score (range 0-110)

9.7 ± 0.72
Loss of smell VAS score (maximum score, 10)

[a]All values are means unless otherwise noted.
[b]Study eligibility criteria did not require a specific baseline blood eosinophil level.
[c]Any asthma severity.

AERD, aspirin-exacerbated respiratory disease
NPS, Nasal Polyp Score
SCS, systemic corticosteroids
SNOT-22, Sino-Nasal Outcome Test-22
VAS, Visual Analogue Scale

Patient Disposition



[a]Randomized and took at least 1 dose of study medication.
[b]24 patients discontinued treatment but completed off-treatment assessments (7 patients receiving mepolizumab and 17 patients receiving placebo). 1 patient receiving mepolizumab completed treatment but did not complete assessments.

Discontinued Study Treatment

- Rates of study treatment discontinuation were 11% (23/206) for mepolizumab and 17% (34/201) for placebo
- Primary reasons for study treatment discontinuation were similar across treatment groups; the most common reasons were:
  - Withdrawal by patient, 6% (12/206) for mepolizumab and 7% (15/201) for placebo
  - Lack of efficacy, 3% (5/206) for mepolizumab and 5% (11/201) for placebo
  - Adverse event, 2% (4/206) for mepolizumab and 2% (4/201) for placebo

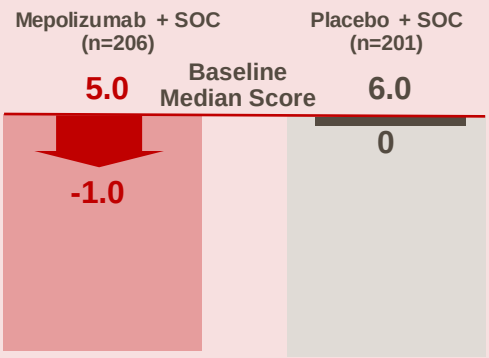
ITT, intent to treat

Co-primary Endpoints

- Mepolizumab significantly improved nasal polyp size (total endoscopic NPS) and nasal obstruction (nasal obstruction VAS score)

Total Endoscopic NPS (Week 52)

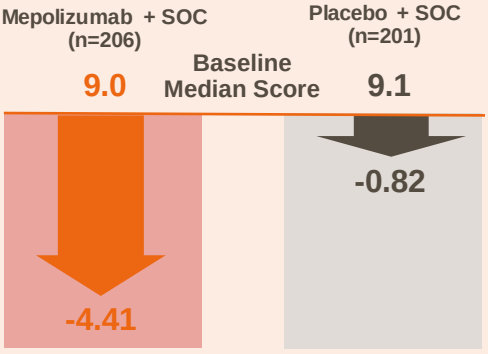
Median Change from Baseline



Difference in medians:
-0.73 (-1.11, -0.34), *P*<0.0001

Nasal Obstruction VAS Score (Weeks 49–52)

Median Change from Baseline



Difference in medians:
-3.14 (-4.09, -2.18), *P*<0.0001

Additional Analyses of Co-primary Endpoints: Change from Baseline

Total Endoscopic NPS (Week 52)

50% (104/206) of mepolizumab patients had **≥1-point improvement** compared with 28% (57/201) of placebo patients

36% (74/206) of mepolizumab patients had **≥2-point improvement** compared with 13% (26/201) of placebo patients

Nasal Obstruction VAS Score (Weeks 49–52)

71% (146/206) of mepolizumab patients had **≥1-point improvement** compared with 50% (100/201) of placebo patients

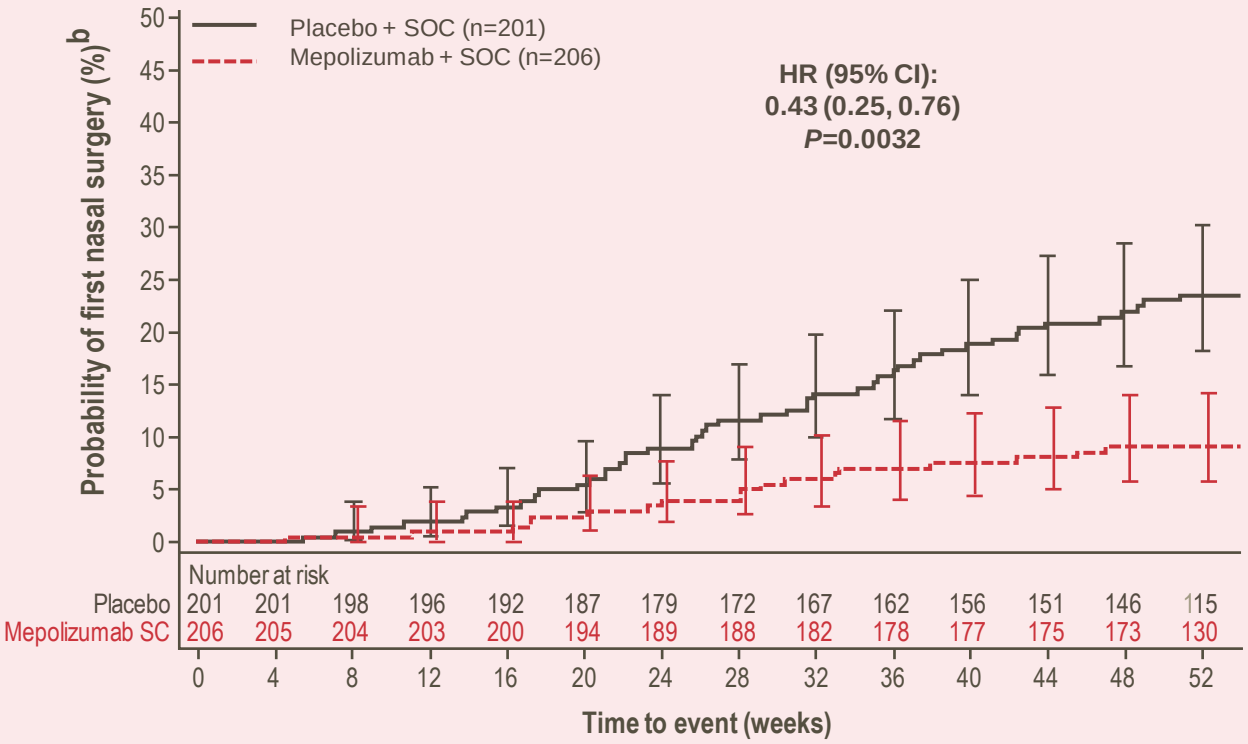
60% (124/206) of mepolizumab patients had **≥3-point improvement** compared with 36% (73/201) of placebo patients

BEC, blood eosinophil count
CI, confidence interval
NPS, Nasal Polyp Score
SOC, standard of care
VAS, Visual Analogue Scale

Time to First Nasal Surgery

- **Key Secondary Endpoint:** Time to first nasal surgery (polypectomy) was statistically significantly longer, with mepolizumab showing a 57% reduction in the risk of repeat surgery vs placebo up to Week 52 (HR [95% CI]: 0.43 [0.25, 0.76], *P*=0.0032)
- At Week 52, 9% (18/206) of patients treated with mepolizumab vs 23% (46/201) of patients on placebo had confirmed surgery (descriptive data)
- Additionally, a post-hoc analysis showed:
  - A subgroup of patients with blood eosinophils ≥300 cells/µL had a 69% reduction in the risk of repeat surgery vs placebo (HR [95% CI]: 0.31 [0.15, 0.64]; mepolizumab + SOC, n=10/139; placebo + SOC, n=35/139)
  - A subgroup of patients with blood eosinophils <300 cells/µL had a 17% reduction in the risk of repeat surgery vs placebo (HR [95% CI]: 0.83 [0.33, 2.09]; mepolizumab + SOC, n=8/67; placebo + SOC, n=11/62)

Time to First Nasal Surgery[a]

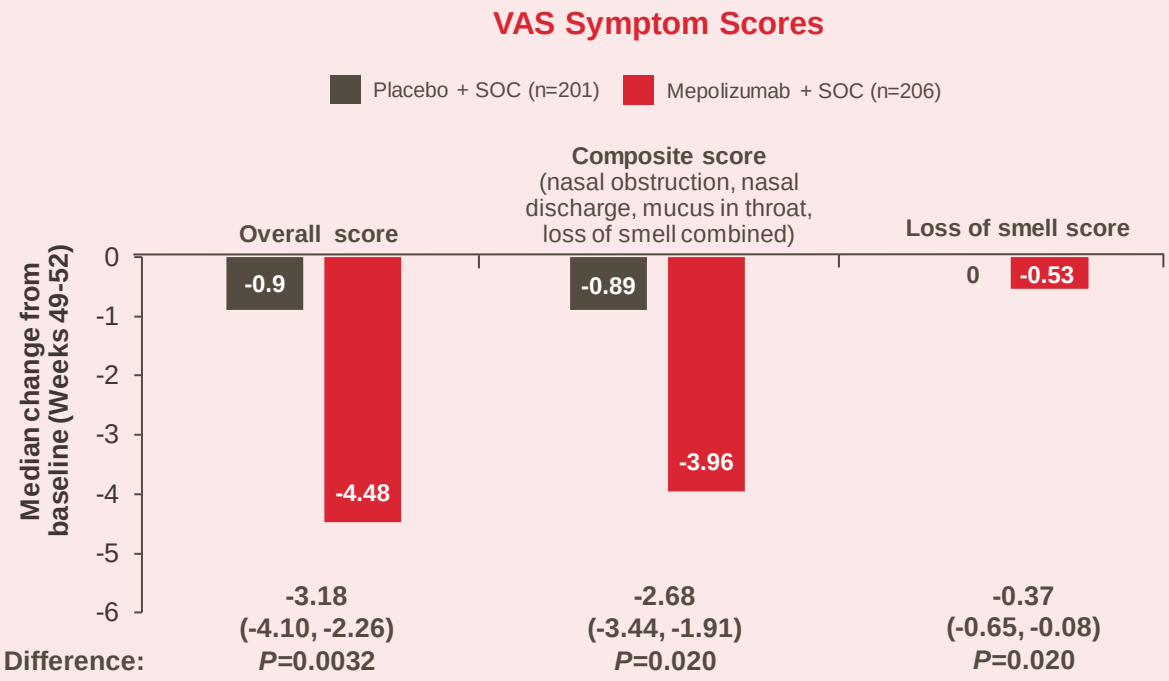


[a]Defined as any procedure involving instruments with resulting incision and removal of polyp tissue [polypectomy] in the nasal cavity or sinuses.
[b]Kaplan-Meier plot.

CI, confidence interval
HR, hazard ratio
OR, odds ratio
SC, subcutaneous
SOC, standard of care

Change From Baseline in VAS Symptom Scores

- **Secondary endpoints:** During Weeks 49-52, patients who received mepolizumab had statistically significant improvement in median change from baseline in overall, composite, and loss of smell VAS scores compared with placebo patients



- Additional pre-specified analysis: During Weeks 49-52, improvements in loss of smell were greater in patients with fewer previous surgeries (Table 1)

Table 1. Change From Baseline in Loss of Sense Smell VAS Score at Weeks 49-52, by Number of Previous Surgeries

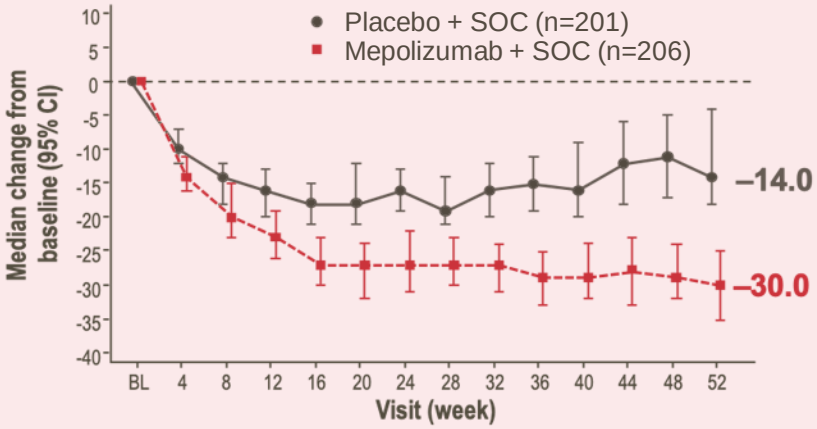
	Patients, n (%)		
	Placebo + SOC (n=201)	Mepolizumab 100 mg SC + SOC (n=206)	Difference in medians (95% CI)
1 Previous Surgery, n	81	108	–
Median change from baseline	-0.07	-1.87	-1.29 (-2.27, -0.31)
2 Previous Surgeries, n	47	47	–
Median change from baseline	-0.02	-0.48	-0.23 (-0.83, 0.37)
>2 Previous Surgeries, n	73	51	–
Median change from baseline	0.00	-0.07	-0.07 (-0.19, 0.05)

CI, confidence interval
SC, subcutaneous
SOC, standard of care
VAS, Visual Analogue Scale

Change From Baseline in SNOT-22 Score

- **Secondary Endpoint:** At Week 52, mepolizumab demonstrated a statistically significant improvement in health-related quality of life as measured by SNOT-22 total score compared with placebo (*P*=0.0032)
- In a post-hoc analysis, 73% (150/205) of patients receiving mepolizumab had a clinically important difference (≥8.9 points as a responder rate analysis) vs 54% (106/198) receiving placebo (OR [95% CI], 2.44 [1.60, 3.73])

SNOT-22 Total Score

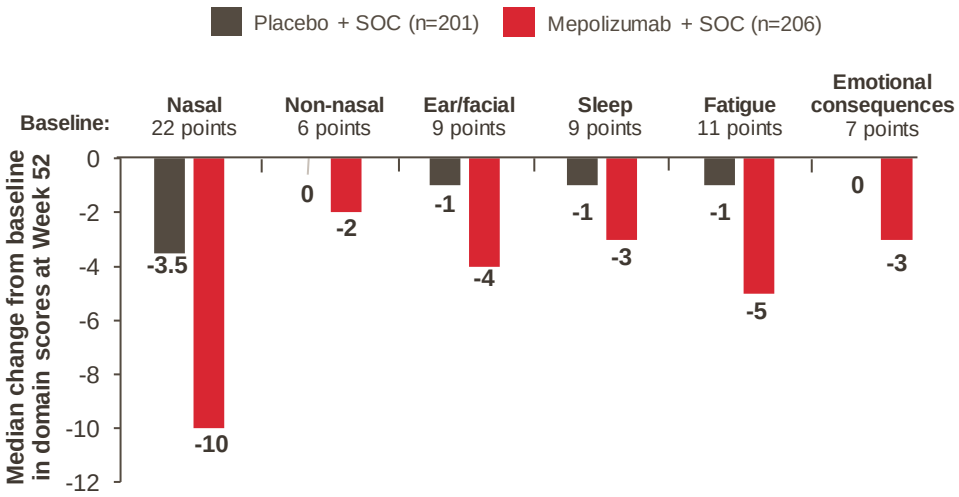


Difference in medians:
-16.49 (-23.57, -9.42)
***P*=0.0032**

Change From Baseline in SNOT-22 Domain Score

- Improvement was seen in all 6 SNOT-22 domains

SNOT-22 Domain Scores



[a]Patients answer 22 individual questions; however, analysis of the SNOT-22 questionnaire is not designed to measure a change in each individual question.

SNOT-22 Domains[a]

Nasal (0-30 points)
- Need to blow nose
- Nasal blockage
- Sneezing
- Runny nose
- Thick nasal discharge
- Decreased sense of smell/taste

Non-nasal (0-10 points)
- Cough
- Post-nasal discharge

Ear/facial (0-20 points)
- Ear fullness
- Dizziness
- Ear pain
- Facial pain

Sleep (0-15 points)
- Difficulty falling asleep
- Wake up at night
- Lack of good night's sleep

Fatigue (0-20 points)
- Wake up tired
- Fatigue
- Reduced productivity
- Reduced concentration

Emotional consequences (0-15 points)
- Frustration/restless/irritable
- Sad
- Embarrassed

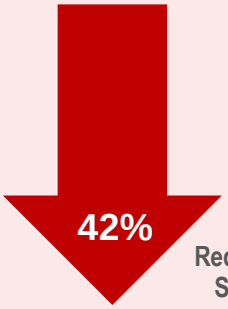
CI, confidence interval
SC, subcutaneous
SNOT-22, Sino-Nasal Outcome Test-22
SOC, standard of care

Proportion of Patients Requiring SCS for Nasal Polyps

- **Secondary Endpoint:** Mepolizumab demonstrated a 42% reduction in the need for SCS vs placebo (OR [95% CI]: 0.58 [0.36, 0.92]; *P*=0.020)
- Over the 52-week period, 25% (52/206) of patients treated with mepolizumab compared with 37% (74/201) in the placebo group required ≥1 course of SCS for treatment of nasal polyps (descriptive)
- Additionally, a post-hoc analysis showed:
  - A subgroup of patients with blood eosinophils ≥300 cells/µl had a 51% reduction in use of SCS vs placebo (HR [95% CI]: 0.49 [0.28, 0.86]; mepolizumab + SOC, n=37/139; placebo + SOC, n=58/139)
  - A subgroup of patients with blood eosinophils <300 cells/µL had a 12% reduction in the risk of reduction in use of SCS vs placebo (HR [95% CI]: 0.88 [0.36, 2.16]; mepolizumab + SOC, n=15/67; placebo + SOC, n=16/62)

Systemic Corticosteroid Use for Nasal Polyps

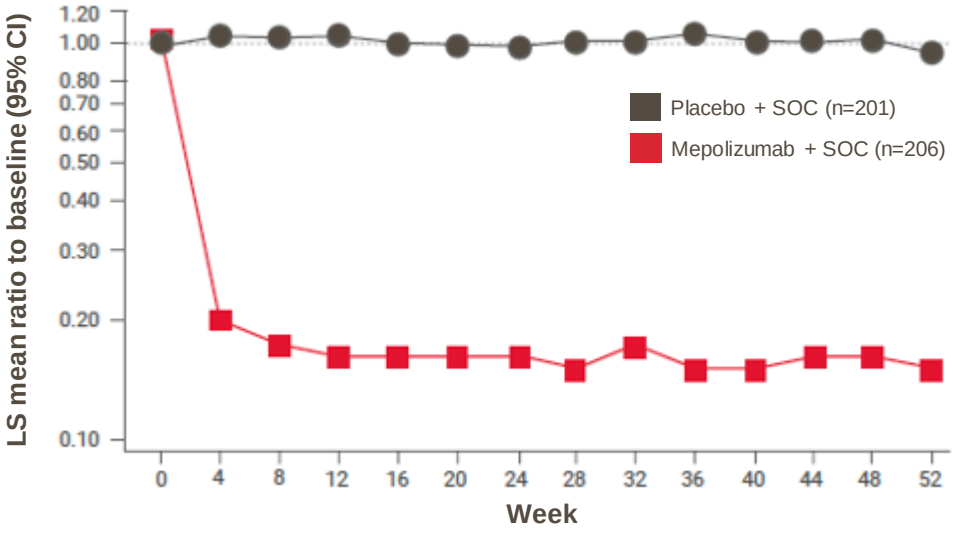
Odds ratio (95% CI): 0.58 (0.36, 0.92)
***P*=0.020**



Reduction in use of SCS vs placebo

Pharmacodynamic Results: Reduction in Blood Eosinophils

- Patients treated with mepolizumab had an 81% reduction in blood eosinophil count compared with placebo at Week 4 that was sustained through Week 52 (ratio 0.19 [95% CI: 0.17, 0.22])



At **Week 52,** the geometric mean BEC in the **mepolizumab** group showed a decline from baseline to **60 cells/µL** compared with a slight decline in the placebo group to 360 cells/µL.[a]

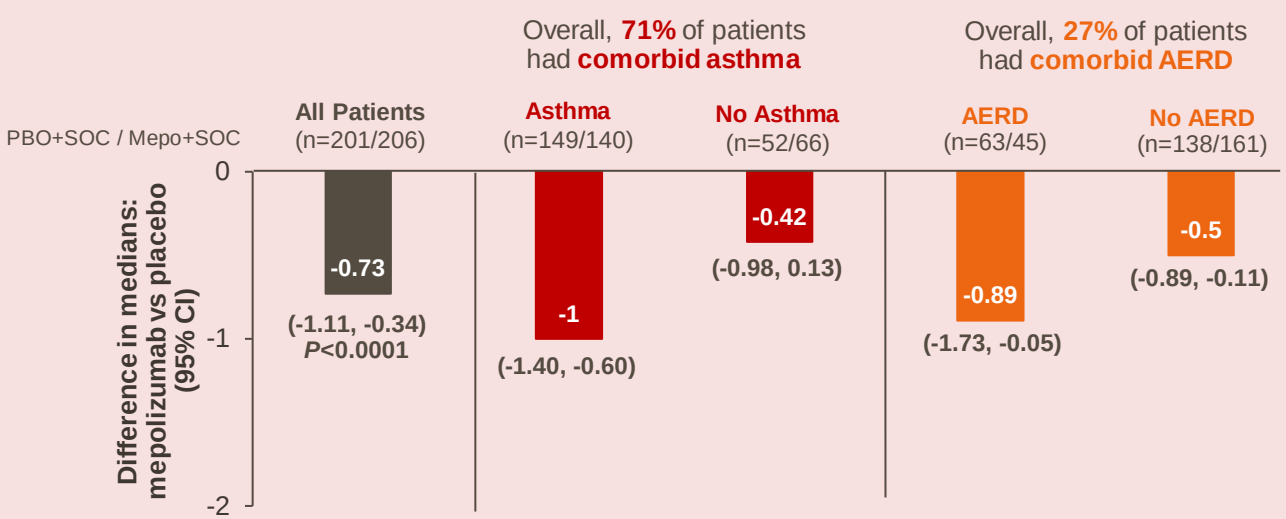
[a]At baseline, geometric mean BEC levels were similar in the mepolizumab (390 cells/µL) and placebo (400 cells/µL) groups.

BEC, blood eosinophil count
CI, confidence interval
HR, hazard ratio
LS, least squares
OR, odds ratio
SCS, systemic corticosteroids
SOC, standard of care

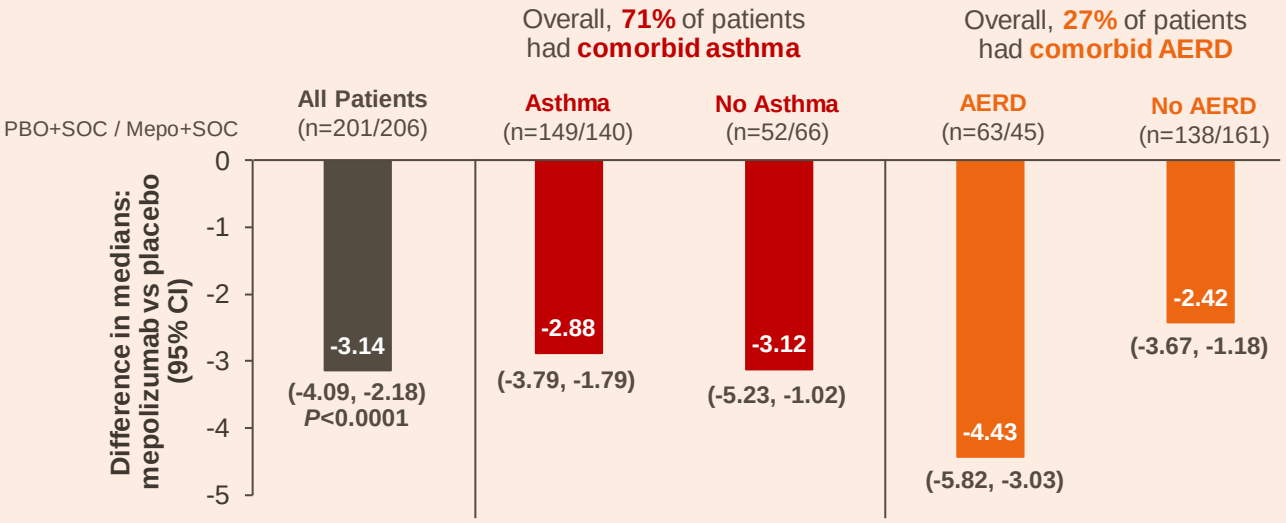
Subgroup Analysis of Co-primary Endpoints: Improvements in Patients with Nasal Polyps With Comorbid Respiratory Diseases

- In patients with **comorbid asthma**[a] and **comorbid AERD**, prespecified analyses showed improvements in the co-primary endpoints consistent with those seen in the overall population in the patients who received mepolizumab compared with placebo

Improvement in Total Endoscopic NPS



Improvement in Nasal Obstruction Symptoms



[a]Mean ACQ-5 scores at baseline were similar in treatment groups (mepolizumab, 2.38; placebo, 2.15) and indicated that patients' asthma was poorly controlled (>1.5).

ACQ, Asthma Control Questionnaire
AERD, aspirin-exacerbated respiratory disease
CI, confidence interval
LS, least squares
Mepo, mepolizumab
NPS, Nasal Polyp Score
PBO, placebo
VAS, Visual Analogue Scale

Key Safety Results

- No additional adverse reactions were identified to those reported in the severe asthma trials
- The most frequent on-treatment AEs were nasopharyngitis, headache, epistaxis, and sinusitis (see Table 3)

SYNAPSE Safety Results

Table 2. Summary of AEs, Systemic or Local Injection-site Reactions, and SAEs

Adverse Event Type	Patients, n (%)	
	Placebo + SOC (n=201)	Mepolizumab 100 mg SC + SOC (n=206)
Any Adverse Event (AE)	**168 (84)**	**169 (82)**
AE related to study treatment	19 (9)	30 (15)
AE leading to treatment discontinuation	4 (2)	4 (2)
AE leading to study withdrawal	1 (1)	0
Systemic or Local Injection-site Reactions		
Systemic reaction	1 (1)	2 (1)
Local injection-site reaction	2 (1)	5 (2)
Anaphylaxis	0	0
Any Serious Adverse Event (SAE)	**13 (6)**	**12 (6)**
Treatment-related SAE	1 (1)	0
Fatal SAE[a]	1 (1)	0

[a]One death (due to myocardial infarction) was reported in the placebo group; this was not considered related to treatment.

Table 3. Summary of Most Frequent On-Treatment AEs[a]

Adverse Event (AE)	Patients, n (%)	
	Placebo + SOC (n=201)	Mepolizumab 100 mg SC + SOC (n=206)
Nasopharyngitis	46 (23)	52 (25)
Headache	44 (22)	37 (18)
Epistaxis	18 (9)	17 (8)
Sinusitis	22 (11)	10 (5)
Back pain	14 (7)	15 (7)
Acute sinusitis	13 (6)	13 (6)
Oropharyngeal pain	10 (5)	16 (8)
Upper respiratory tract infection	14 (7)	12 (6)
Nasal polyps	16 (8)	8 (4)
Bronchitis	13 (6)	10 (5)
Asthma	18 (9)	4 (2)
Cough	13 (6)	7 (3)
Arthralgia	5 (2)	13 (6)
Otitis media	10 (5)	5 (2)

[a]Reported in ≥5% of patients in any treatment group.

AE, adverse event **SC**, subcutaneous **SOC**, standard of care

Key Safety Results (continued)

- In patients with severe CRSwNP receiving 100 mg of mepolizumab up to Week 52
  - 6 (3%) patients in the mepolizumab group and 1 (<1%) in the placebo group had detectable anti-mepolizumab antibodies
  - No neutralizing antibodies were detected in any patients

Summary of SYNAPSE Trial

- This randomized, double-blind, placebo-controlled, phase 3 trial evaluated the efficacy and safety of mepolizumab 100 mg added to standard-of-care therapy in adult patients with recurrent, refractory, severe, bilateral CRSwNP who were eligible for repeat surgery
  - The patient population in SYNAPSE reflects patients who may be candidates for biologic treatment based on the EUFOREA and EPOS2020 guidelines
- All primary and secondary endpoints were met with statistical significance. Compared with placebo, mepolizumab plus standard-of-care therapy significantly:
  - Improved NPS and nasal obstruction VAS scores
  - Reduced the risk of nasal surgery and the need for SCS
  - Improved sino-nasal symptoms (VAS), including loss of smell
  - Improved HRQoL (SNOT-22)
- Treatment effects were sustained until Week 52 for all endpoints
- No additional adverse reactions were identified to those reported in the severe asthma trials
- Most common AEs (≥10% in either group) were nasopharyngitis, headache, and sinusitis

AEs, adverse events
CRSwNP, chronic rhinosinusitis with nasal polyps
EPOS2020, European Position Paper on Rhinosinusitis and Nasal Polyps 2020
EUFOREA, European Forum for Research and Education in Allergy and Airway Diseases
HRQoL, health-related quality of life
NPS, Nasal Polyp Score
SCS, systemic corticosteroids
SNOT-22, Sino-Nasal Outcome Test-22
VAS, Visual Analogue Scale