Mepolizumab for Chronic Rhinosinusitis With Nasal Polyps: Comorbid Asthma, NSAID Exacerbated Respiratory Disease, Eosinophil Stratification

Poster No. P503

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Background

CRSwNP is a subtype of CRS and is characterized by eosinophilic inflammation resulting in outgrowths of sinonasal tissue,[1–4] frequently involving type 2 inflammatory mediators, such as IL-5.[4]

CRSwNP symptoms include nasal blockage, facial pressure, loss of sense of smell and rhinorrhea.[5,6] Current standard of care includes intranasal corticosteroids and short courses of SCS to maintain disease control.[1,6] Further treatment options include nasal surgery, the success of which is often short-lived.[6]

Mepolizumab, a targeted, humanized monoclonal antibody that binds to and inactivates IL-5,[7] has shown promise for managing recurrent nasal polyps.[4,8] It is approved for the treatment of severe eosinophilic asthma, EGPA and HES in multiple countries worldwide.[9,10]

SYNAPSE, a Phase III study, assessed the efficacy and safety of 4-weekly add-on mepolizumab 100 mg SC, in adults with CRSwNP in need of repeat surgery. In the setting of the SYNAPSE study, we investigated the efficacy of mepolizumab by the following clinically important subgroups of patients:

Comorbid asthma | Comorbid N-ERD | Baseline BEC

Methods

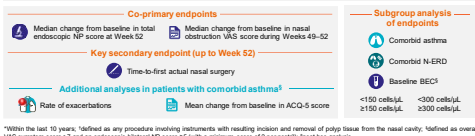
Study design
GSK ID: 205687/NCT03085797

Randomized | Double-blind | Placebo-controlled | Parallel-group

Phase III trial

Eligibility criteria

- ≥18 years of age
- ≥1 prior* surgery†
- Need for surgery‡
- Bilateral NP diagnosis
- Obstruction VAS score >5
- Current or former smoker (>6 months)
- No biologic or immunosuppressant treatment
- No pre-existing clinically significant conditions that are uncontrolled with standard treatment
- No SCS use <4 weeks prior to screening



Co-primary endpoints
- Median change from baseline in total endoscopic NP score at Week 52
- Median change from baseline in nasal obstruction VAS score during Weeks 49–52

Key secondary endpoint (up to Week 52)
- Time-to-first actual nasal surgery

Additional analyses in patients with comorbid asthma§
- Rate of exacerbations
- Mean change from baseline in ACQ-5 score

Subgroup analysis of endpoints
- Comorbid asthma
- Comorbid N-ERD
- Baseline BEC§

<150 cells/μL ≥150 cells/μL | <300 cells/μL ≥300 cells/μL

*Within the last 10 years; †defined as any procedure involving instruments with resulting incision and removal of polyp tissue from the nasal cavity; ‡defined as overall VAS symptom score >7 and an endoscopic bilateral NP score ≥5 (with a minimum score of 2 per nostril); §post hoc analysis.

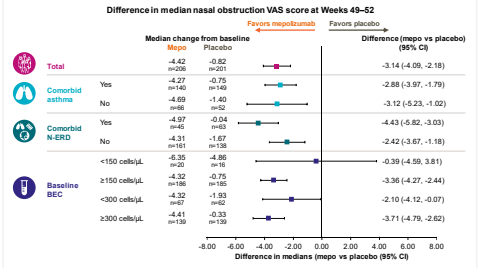
Results

Baseline demographics and characteristics (N=407)

Age, years, mean (SD)	48.8 (13.0)
Female, n (%)	143 (35)
Duration of NP, years, mean (SD)	11.4 (8.4)
Patients with asthma, n (%)	289 (71)
Patients with N-ERD, n (%)	108 (27)
Prior NP surgeries*, n (%)	≥1 407 (100); ≥2 218 (54); ≥3 124 (30); ≥4 62 (15); ≥5 37 (9)
Total endoscopic score, median (range) (scale: 0–8)†	5.0 (0–8)
Nasal obstruction VAS score, median (range) (scale: 0–10)†	9.1 (5.3–10.0)
BEC, cells/μL, geo. mean (SD log)	390 (0.764)
Courses of OCS‡, n (%)	0 210 (52); 1 111 (27); 2 35 (9); >2 51 (13)
Patients with exacerbations§, n (%)	58 (20)
ACQ-5 score§, Mean (SD)	2.3 (1.4)
Time since last NP surgery* years, mean (SD) [range]	4.02 (2.7) [0.0–10.7]

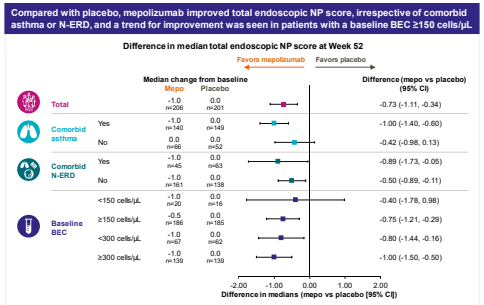
*In the previous 10 years; †higher scores indicate greater disease severity or worse quality of life; ‡for NP treatment in the previous 12 months, §for patients with asthma.

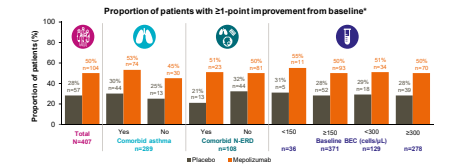
Mepolizumab improved nasal obstruction VAS score compared with placebo, especially in patients with comorbid N-ERD or a baseline BEC ≥150 cells/μL



ITT; median difference in change from baseline for mepolizumab versus placebo estimated using quantile regression with covariates of treatment group, region, baseline score and $\log_2$ baseline BEC (except in the analysis by baseline BEC).

Compared with placebo, mepolizumab improved total endoscopic NP score, irrespective of comorbid asthma or N-ERD, and a trend for improvement was seen in patients with a baseline BEC ≥150 cells/μL





ITT; difference in median change from baseline for mepolizumab versus placebo estimated using quantile regression with covariates of treatment group, region, baseline score and $\log_2$ baseline BEC (except in the analysis by baseline BEC); *in the absence of surgery/sinuplasty prior to that visit.

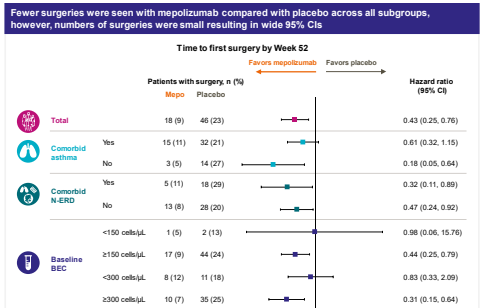
In patients with comorbid asthma, exacerbation rates were lower and mean ACQ-5 score improved with mepolizumab compared with placebo

Rate of exacerbations
Reduced by 67% (rate ratio mepo vs placebo [95% CI]: 0.33 [0.12, 0.95])

ACQ-5 score at Week 52
Improved by 0.66 points compared to placebo (MCID* ≥0.5)
LS mean difference mepo vs placebo [95% CI]: -0.66 [-0.92, -0.40])

ITT; rate ratio (95% CI) from a negative binomial model with covariates of treatment group, geographic region, $\log_e$ baseline BEC and number of exacerbations in the previous year (0, 1, ≥2 as ordinal), and with logarithm of time (year) on-study up to Week 52 as an offset variable; LS mean change from baseline for mepolizumab versus placebo estimated using mixed model repeated measures with covariates of treatment group, geographic region, baseline, $\log_2$ baseline BEC, visit plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions; *MCID was a ≥0.5 decrease in total score.[11]

Fewer surgeries were seen with mepolizumab compared with placebo across all subgroups, however, numbers of surgeries were small resulting in wide 95% CIs



ITT; Kaplan–Meier estimates of probability of event; hazard ratio (95% CI) from Cox proportional hazards model with covariates of treatment group, geographic region, baseline total endoscopic score (centrally read), baseline nasal obstruction VAS score, $\log_2$ baseline BEC (except in analyses by baseline BEC) and number of previous surgeries (1, 2, >2 as ordinal).

Conclusions

- In patients with CRSwNP requiring further surgery, despite standard of care therapy, 4-weekly add-on mepolizumab 100 mg SC improved NP score and nasal obstruction and reduced the risk of sinus surgeries irrespective of comorbid asthma or N-ERD.
- As mechanistically expected, mepolizumab efficacy was higher in patients with higher BEC.
- These data suggest that mepolizumab is efficacious for the treatment of CRSwNP, particularly in patients with BEC ≥150 cells/μL.

Abbreviations

ACQ, asthma control questionnaire; BEC, blood eosinophil count; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; EGPA, eosinophilic granulomatosis with polyangiitis; geo, geometric; IL, interleukin; ITT, intention-to-treat; LS, least squares; MCID, minimal clinically important difference; mepo, mepolizumab; MF, mometasone furoate; N-ERD, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; OCS, oral corticosteroids; SC, subcutaneous; SCS, systemic corticosteroids; SD, standard deviation; VAS, visual analog scale.

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