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

**Background**

**CISSNP** is a subtype of CRS and is characterized by eosinophilic inflammation resulting in uncontrolled nasal tissue. Typically involving type 2 inflammatory markers, such as IL-5.

**CISSNP** symptoms include nasal blockage, facial pressure, loss of sense of smell, and mucosal inflammation. Current standard of care includes intranasal corticosteroids and short courses of ICS to manage disease control.**1** Further treatment options include nasal surgery, the success of which is often uncertain.

Mepolizumab, a targeted, humanized monoclonal antibody that binds to and inactivates IL-5, has shown promise for managing recurrent nasal polyps.**1** It is approved for treatment of severe eosinophilic asthma, ECR and RH in multiple countries worldwide.

**SYNAPSE**, a Phase II study, assessed the efficacy and safety of 4-weekly add-on mepolizumab 100 mg SC. In eligible patients with CISSNP, it is now pivotal 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**

- Open-label, randomized, double-blind trial
- Placebo-controlled, parallel-group design
- Patients randomized to receive mepolizumab (n=289) or placebo (n=206)
- Regional centers (n=18 countries worldwide)

**Objective**

- Investigate the efficacy of mepolizumab by clinical characteristics of comorbid asthma and nonsteroidal anti-inflammatory drug (NSAID)–exacerbated respiratory disease (N-ERD) patients
- Main efficacy endpoints: nasal polyposis polyp tissue from the nasal cavity
- Secondary endpoints: symptom scores, health-related quality of life (HRQoL), etc.

**Randomization and blinding**

- Randomization to treatment groups was performed centrally based on a permuted block design
- Investigator and participants were blinded to treatment allocation
- Independent data monitoring committee monitored the study

**Endpoints**

- **Primary endpoint**: median change from baseline VAS symptom score during Weeks 49-52
- **Co-primary endpoints**: proportion of patients with 
  - **ACQ-5 score**: 
    - Favors placebo: 0.18 (95% CI: 0.05, 0.64)
  - **BEC**: 
    - Favors placebo: 0.31 (95% CI: 0.15, 0.64)
  - **N-ERD**: 
    - Favors placebo: 0.83 (95% CI: 0.33, 2.09)
  - **Comorbid asthma**: 
    - Favors placebo: 0.47 (95% CI: 0.24, 0.92)

**Exacerbations**

- Exacerbations were defined as any procedure involving instruments with resulting incision and removal of polyp tissue from the nasal cavity

**Duration of follow-up**

- Patients were followed for 52 weeks after randomization

**Comorbid conditions**

- Comorbid asthma: for patients with comorbid asthma, exacerbation rates were lower and mean ACQ-5 score improved 
- Comorbid N-ERD: for patients with a baseline BEC ≥150 cells/µL, a trend for improvement was seen in patients with a baseline BEC ≥150 cells/µL
- Baseline BEC: in the analysis by baseline BEC; in the absence of surgery/sinuplasty prior to that visit.

**Results**

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Placebo</th>
<th>Mepolizumab</th>
<th>Difference (mepo vs placebo) (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Comorbid asthma</td>
<td></td>
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**Conclusion**

- In patients with CISSNP requiring further surgery, despite standard 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 elevated BEC.

- These data suggest that mepolizumab is efficacious for the treatment of CISSNP, particularly in patients with BEC ≥150 cells/µL.