Efficacy and Safety of Mepolizumab in Hypereosinophilic Syndrome: a Phase III, Randomized, Placebo-Controlled Trial

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Background

Hypereosinophilic syndrome (HES) is a rare group of disorders, characterized by elevated eosinophil levels in the blood and/or tissues and eosinophil-mediated tissue/organ damage and dysfunction.[1]

Mepolizumab is a humanized anti-interleukin 5 monoclonal antibody approved for use in patients with other eosinophilic diseases, such as severe eosinophilic asthma (100 mg administered subcutaneously [SC]) and eosinophilic granulomatosis with polyangiitis (300 mg SC).[2]

In previous clinical studies of patients with HES, mepolizumab (750 mg administered intravenously) reduced blood eosinophil counts and had an oral corticosteroid sparing effect.[3-5] However, the impact of mepolizumab on HES disease activity is unclear.

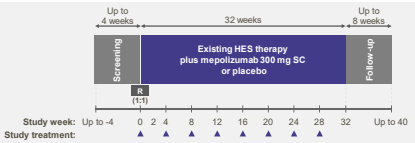
The aim of this study was to investigate the clinical efficacy and safety of mepolizumab 300 mg SC versus placebo in patients with HES.

Methods

Study design

GSK ID: 200622; NCT02836496

Randomized | Double-blind | Multicenter | Placebo-controlled | Parallel-group | Phase III trial



Patient eligibility criteria

- ≥12 years of age
- Diagnosis of FIP1L1-PDGFRA-negative HES* ≥6 months previously
- Receiving a stable dose of HES therapy† ≥4 weeks before the baseline visit
- Uncontrolled HES (≥2 flares within the past 12 months and a blood eosinophil count ≥1000 cells/µL at screening)

Methods (continued)

Study endpoints

Primary endpoint

The proportion of patients who experienced a flare during the 32-week study period
- Flares were defined as:
  a) A HES-related clinical manifestation (based on a physician-documented change in clinical signs or symptoms) that required either an increased dose of maintenance OCS ≥10 mg prednisone equivalent/day for 5 days or an increase in/addition of any cytotoxic and/or immunosuppressive HES therapy
  b) Receipt of ≥2 courses of blinded OCS during the treatment period

Secondary endpoints

Time to first flare (allowing assessment of the probability of first flare over time)
Annualized rate of flares
The proportion of patients who experienced a flare during study Weeks 20–32

Other endpoints

Ratio to baseline blood eosinophil count
Frequency of AEs and SAEs

For the duration of the trial, investigators, GSK staff, and patients were all blinded to the study treatment, absolute blood eosinophil counts, total white blood cell counts, and white blood cell differentials. Separate GSK staff (not involved in other aspects of the trial) monitored blood eosinophil counts and initiated blinded OCS treatment if they reached a pre-specified threshold (2x value at baseline, or value at baseline + 2500 cells/µL). *FIP1L1-PDGFRA* is a fusion gene that causes clonal eosinophil expansion. After Week 32, patients were eligible to continue receiving mepolizumab 300 mg SC every 4 weeks as part of an open-label extension study. †HES diagnosis was based on organ system involvement and/or dysfunction that could be directly related to a blood eosinophil count >1500 cells/µL on ≥2 occasions, and/or tissue eosinophilia, without a discernible secondary cause; ‡HES therapy could include (but was not limited to) OCS, immunosuppressive, and cytotoxic therapy. R, randomization

Results

- 141 patients were screened for eligibility and 108 were randomized. Overall, 4 patients (2 per treatment group) withdrew from the study before Week 32; 2 additional patients (1 per treatment group) discontinued treatment.

Patient population

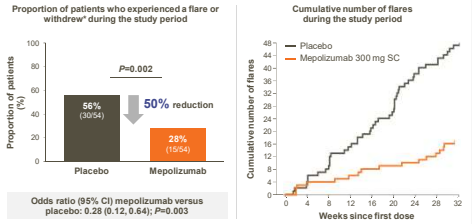
	Placebo (N=54)	Mepolizumab (N=54)
Age mean (range) years	45 (15–80)	47 (12–82)
Female n (%)	27 (50)	30 (56)
HES duration mean (SD) years	5.7 (8.04)	5.5 (5.08)
BMI mean (SD) kg/m²	26.20 (5.934)	26.38 (5.885)
Blood eosinophil count geometric mean (SD of log) cells/µL	1350 (0.708)	1460 (0.946)

BMI, body mass index; SD, standard deviation

In the placebo arm
70% of patients were using OCS and **17% of patients** were receiving cytotoxic/immunosuppressive therapy at baseline

In the mepolizumab arm
74% of patients were using OCS and **26% of patients** were receiving cytotoxic/immunosuppressive therapy at baseline

The occurrence of flares decreased with mepolizumab versus placebo across the full study period

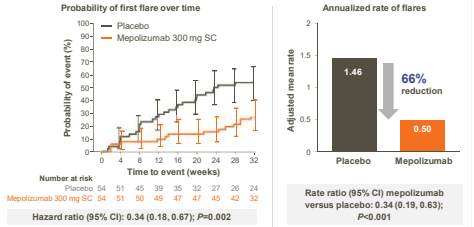


Odds ratio (95% CI) mepolizumab versus placebo: 0.28 (0.12, 0.64); *P*=0.003

*2 patients in the placebo arm and one patient in the mepolizumab arm had no flare but withdrew from the study. CI, confidence interval

- The occurrence of flares also decreased with mepolizumab versus placebo during Weeks 20–32.

The risk of experiencing a flare and the annualized rate of flares were both 66% lower with mepolizumab versus placebo over the study period



Hazard ratio (95% CI): 0.34 (0.18, 0.67); *P*=0.002

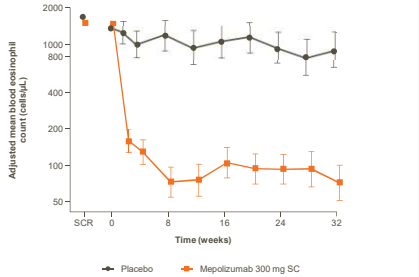
Rate ratio (95% CI) mepolizumab versus placebo: 0.34 (0.19, 0.63); *P*<0.001

Vertical bars represent 95% CI.

Conclusions

- This randomized, placebo-controlled, Phase III study demonstrated that treatment with mepolizumab (300 mg SC) was associated with a 50% reduction in the occurrence of flares compared with standard of care plus placebo, in patients with uncontrolled HES.
- The risk of a flare and the annualized rate of flares were both 66% lower during the study period for patients receiving mepolizumab versus placebo; no new safety signals were identified with mepolizumab.
- Mepolizumab is the first treatment shown to reduce disease flares in patients with *FIP1L1-PDGFRA*-negative HES and the findings from this study represent an important advance for the management of this rare, debilitating disease.

Blood eosinophil counts were markedly reduced with mepolizumab versus placebo



- Frequencies of AEs were generally similar between patients receiving mepolizumab and placebo (data not shown).

References

1. Curtis C et al. *Clin Rev Allergy Immunol* 2016;50:240–51.
2. Mepolizumab (NUCALA) highlights of prescribing information. 2019. Available from: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL.PDF [last accessed March 2020].
3. Rothenberg ME et al. *N Engl J Med* 2008;358:1215–28.
4. Roufosse F et al. *J Allergy Clin Immunol* 2010;126:828–35 e3.
5. Roufosse FE et al. *J Allergy Clin Immunol* 2013;131:461–7 e1-5.

Disclosures

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