Safety and Efficacy of Mepolizumab in Hypereosinophilic Syndrome: An Open-Label Extension Study

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Aims

HES is a heterogeneous disorder characterized by elevated eosinophil counts in peripheral blood and/or tissues, marked deposition of eosinophil granule proteins in tissues, and eosinophil-mediated organ damage.[1,2]

Treatment options for *FIP1L1-PDGFRA*-negative HES include OCS and cytotoxic and/or immunosuppressive agents, which can fail to achieve complete disease remission and can have significant dose limiting side effects.[3-5]

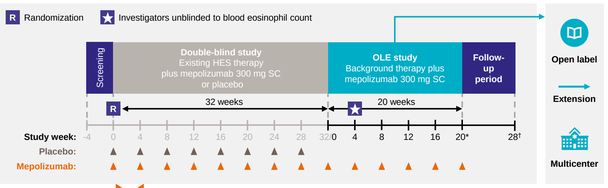
Mepolizumab, a humanized, monoclonal anti–interleukin-5 antibody, has recently been approved for the treatment of patients with HES,[6] based on the results of the Phase III 200622 study (NCT02836496). This study demonstrated that mepolizumab significantly reduced disease flares and blood eosinophil counts versus placebo, with a favorable safety profile in patients with uncontrolled *FIP1L1-PDGFRA*-negative HES.[7]

This OLE study aimed to further investigate the safety and efficacy of mepolizumab in patients who had previously completed the double-blind 200622 study.

Methods

Study design

Double-blind study: 200622/NCT02836496; OLE study: 205203/NCT03306043



Patient eligibility criteria

For participation in double-blind study:

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

For participation in OLE study:

- **Completed the double-blind study** or prematurely withdrew from study treatment but continued to be assessed until Week 32

OLE study endpoints

Primary endpoints

- Frequency of AEs, SAEs, AESIs, and ADAs

Exploratory endpoints

- Annualized rate of flares, defined as:
  - A worsening of HES-related clinical symptoms and/or an elevated peripheral blood eosinophil count requiring:
    - a) An increase in OCS prednisone-equivalent dose by ≥10 mg/day for ≥5 days OR
    - b) An increase in dose/addition of any cytotoxic or immunosuppressive HES therapy on top of existing HES therapy that had not been reduced in the past 4 weeks
- Proportion of patients receiving OCS during Weeks 0–4 of the OLE study who achieved a ≥50% reduction in mean daily OCS dose from Weeks 0–4 to 16–20 *(Treating investigators could, but were not specifically instructed to, taper OCS dose)*
- Change from baseline in blood eosinophil count

*Patients who continued to receive mepolizumab after the OLE study (via mepolizumab HES extended access program [MHE104317/MHE112562; NCT00244686]) had their last assessment at Week 20; †patients who did not continue to receive mepolizumab after the OLE study had their last follow-up visit at Week 28, 12 weeks after their last dose of mepolizumab.

Results

- Overall, 98% (102/104) of patients who completed the double-blind study enrolled in the OLE study. Among these, 96% (98/102) completed the OLE study.

Patient demographics and characteristics (N=102)

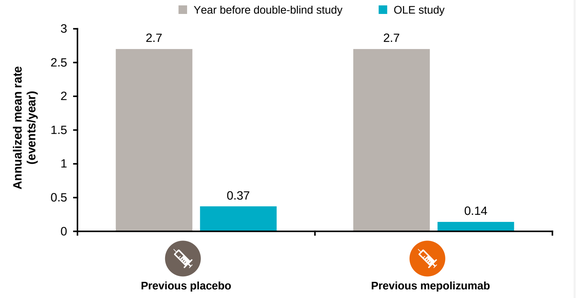
Mean (SD) age:	Female:	Previous treatment in double-blind study:	Mepolizumab exposure (both studies):
46 (16) years	**54%**	**Placebo: n=52** **Mepolizumab: n=50**	**70.0 patient-years**

The safety profile of mepolizumab was consistent with previous reports[7,8]

	Mepolizumab 300 mg SC		
	Previous placebo (n=52)	Previous mepolizumab (n=50)	Total (N=102)
Safety endpoints, n (%)			
Any AEs	40 (77)	26 (52)	66 (65)
On-treatment AEs	38 (73)	24 (48)	62 (61)
Treatment-related* AEs	11 (21)	4 (8)	15 (15)
Leading to study treatment discontinuation	1 (2)	0	1 (<1)
Leading to study withdrawal	1 (2)	0	1 (<1)
Any SAEs	6 (12)	3 (6)	9 (9)
On-treatment SAEs	6 (12)	2 (4)	8 (8)
Treatment-related* SAEs	1 (2)	0 (0)	1 (<1)
Fatal AEs/SAEs	0	0	0
Most frequent† AESIs			
Local injection site reactions‡	3 (6)	3 (6)	6 (6)
All infections§	18 (35)	18 (36)	36 (35)
ADAs			
Baseline	0 (0)	1 (2)	1 (<1)
Other time point	0 (0)	0 (0)	0 (0)

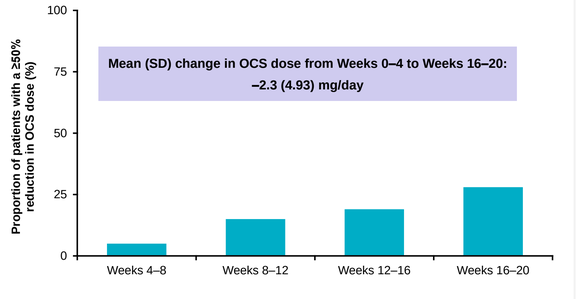
*As determined by the treating investigator; †reported for >5% of patients overall; ‡identified by the investigator in case report forms designed for collecting data on systemic reactions and local injection site reactions; §identified using preferred terms from the Medical Dictionary for Regulatory Activities (V22.1).

The annualized rate of HES flares was reduced from baseline with mepolizumab treatment



In the year before the double-blind study HES flares were defined as a documented HES-related worsening of clinical symptoms and/or blood eosinophil counts that required an escalation in therapy. During the OLE study HES flares were defined as a documented HES-related worsening of clinical symptoms and/or blood eosinophil counts that required a ≥10 mg/day increase from the patient's most recent maintenance OCS dose for ≥5 days, or an increase in/ addition of any cytotoxic and/or immunosuppressive HES therapy from/to the most recent dose of HES therapy.

28% of the patients receiving OCS during Weeks 0–4 of the OLE study* achieved a ≥50% reduction in mean daily OCS dose by Weeks 16–20

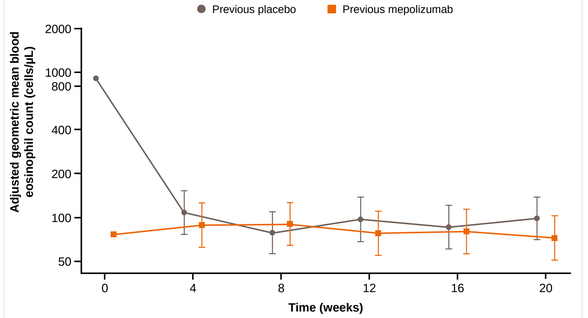


*A total of 73 patients (39 in the previous placebo group and 34 in the previous mepolizumab group) were receiving an OCS dose >0 mg/day during Weeks 0–4.

Conclusions

- Long-term treatment with mepolizumab 300 mg SC plus background therapy has a favorable safety profile, without the development of neutralizing antibodies in patients with HES, consistent with previous reports.[8,9]
- Mepolizumab was associated with reductions from baseline in flare rates and controlled blood eosinophil counts, among patients who previously received mepolizumab or placebo in the double-blind study.
- Mepolizumab was also associated with reductions in OCS use among the total OLE study population.
- These results provide further evidence of the clinical benefit of mepolizumab in patients with uncontrolled *FIP1L1-PDGFRA*-negative HES.

Mepolizumab was associated with controlled blood eosinophil counts in both treatment groups from the previous double-blind study



Abbreviations

ADA, anti-drug antibody; AE, adverse event; AESI, adverse event of special interest; HES, hypereosinophilic syndrome; OCS, oral corticosteroids; OLE, open-label extension; SAE, serious adverse event; SC, subcutaneous, SD, standard deviation.

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Disclosures

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- **GJG** is currently an employee of NexEos Diagnostics, has acted as a consultant for Genentech, GSK, AstraZeneca, and Knopp Biosciences, has received royalties from the Mayo Foundation, and has a royalty sharing agreement with Teva. **FR** reports consultancy fees from AstraZeneca and GSK. **GC** has received advisory board fees, speaking fees, and research grants from GSK, AstraZeneca, Genentech, Sanofi Genzyme, Regeneron, Teva, and Novartis. **SF** has received speaking fees from Vifor Pharma. **BW** has no conflicts to declare. **AR** declares consultancy and advisory board attendance for Novartis, Blueprint, Decipher and Incyte and participation as a trial investigator for GSK, Novartis, Blueprint, Decipher, Incyte, and Gilead. **ESB** is a former employee of GSK and is currently employed by Aeglea BioTherapeutics, Austin, TX, USA; he holds stocks/shares in both companies. **JS**, **JHB**, and **SWY** are all employees of GSK and own stocks/shares.
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