

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



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What is already known about this topic? A phase III study demonstrated that compared with placebo, 4-weekly add-on mepolizumab (300 mg subcutaneously) reduced flares in patients with uncontrolled FIP1-like-1-platelet-derived growth factor receptor α (FIP1L1-PDGFR α)-negative hypereosinophilic syndrome (HES), with a positive benefit–risk profile.

What does this article add to our knowledge? This open-label extension study found no new safety signals with mepolizumab treatment in patients with FIP1L1-PDGFR α -negative HES. Moreover, mepolizumab continued to control flares and blood eosinophil counts after 52 weeks of continuous treatment.

How does this study impact current management guidelines? Findings from this open-label extension study provide further evidence that patients with FIP1L1-PDGFR α -negative HES are likely to benefit from treatment with mepolizumab and may be able to reduce oral corticosteroid use.

BACKGROUND: A double-blind, placebo-controlled, phase III study (200622) showed that mepolizumab reduces disease flares for patients with uncontrolled FIP1-like-1-platelet-derived growth factor receptor α -negative hypereosinophilic syndrome (HES) and two or more flares in the previous year.

OBJECTIVE: To further characterize the safety, clinical benefit, and pharmacodynamics of mepolizumab.

METHODS: Eligible patients from both treatment arms of the double-blind study could enter an open-label extension study

(205203; NCT03306043) to receive 4-weekly mepolizumab (300 mg subcutaneously) plus background therapy for 20 weeks. Primary end points were safety-based; other end points included flare rates and changes from baseline in mean daily oral corticosteroid (OCS) dose and blood eosinophil count.

RESULTS: Of 104 patients who completed the double-blind study, 98% (previous placebo, $n = 52$; previous mepolizumab, $n = 50$) enrolled in the open-label extension. Overall, 66 of patients reported adverse events (AEs) (65%), 15 reported

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Conflicts of interest: G.J. Gleich 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. F. Roufosse reports consultancy fees from AstraZeneca and GSK and royalties from UpToDate. G. Chupp has received advisory board fees, speaking fees, and research grants from GSK, AstraZeneca, Genentech, Sanofi Genzyme, Regeneron, Teva, and Novartis. S. Faguer declares consultancy for Abyonyx Pharma and speaker fees from Vifor Pharma. A. Reiter declares consultancy and advisory board attendance for Novartis, Blueprint, Deciphera, and Incyte and participation as a trial investigator for GSK, Novartis, Blueprint, Deciphera, Incyte, and Gilead. S.W. Yancey, J.H. Bentley, and J. Steinfeld are all employees of GSK and own stocks/shares. B. Walz declares no relevant conflicts of interest.

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Abbreviations used

ADA- Antidrug antibodies
AE- Adverse event
AESI- Adverse event of special interest
EAP- Expanded access program
<i>FIP1L1-PDGFRα</i> - FIP1-like-1-platelet-derived growth factor receptor α
HES- Hypereosinophilic syndrome
OCS- Oral corticosteroid
OLE- Open-label extension
SA- Serious adverse event

treatment-related AEs (15%), and nine reported serious AEs (9%). No events were fatal. The annualized flare rate (95% confidence interval) in the previous placebo and previous mepolizumab groups was 0.37 (0.16-0.86) and 0.14 (0.04-0.49) events/y, respectively. Of 72 patients receiving OCS during weeks 0 to 4, 20 (28%; previous placebo, $n = 14$; previous mepolizumab, $n = 6$) achieved 50% or greater reductions in mean daily dose during weeks 16 to 20. At week 20, blood eosinophil count was reduced by 89% in patients previously receiving placebo and remained reduced for those previously receiving mepolizumab.

CONCLUSIONS: Extended mepolizumab treatment was associated with a positive benefit–risk profile. Continued control of disease flares and blood eosinophil counts, plus reductions in OCS use, were observed with mepolizumab in patients with FIP1-like-1-platelet-derived growth factor receptor α -negative HES. © 2021 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). (J Allergy Clin Immunol Pract 2021;9:4431-40)

Key words: Hypereosinophilic syndrome; Mepolizumab; Anti-IL-5; Safety; Efficacy; Flare; Oral corticosteroid

INTRODUCTION

Hypereosinophilic syndrome (HES) is a heterogeneous disorder characterized by elevated eosinophil counts in the peripheral blood and/or tissues and eosinophil-mediated organ damage that does not result from exogenous, readily detectable underlying causes of hypereosinophilia.¹ Although any tissue or organ system can be affected in HES, eosinophilic infiltration is most commonly observed in the cutaneous, pulmonary, gastrointestinal, cardiovascular, and neurologic organ systems.¹⁻⁵ Disease outcomes for patients with HES often depend on the nature and extent of end-organ damage.^{3,6}

The main goal of HES treatment is to achieve sustained reductions in blood and tissue eosinophil counts, to reverse and prevent further eosinophil-mediated end-organ damage and improve symptoms.² Common treatment options for HES include oral corticosteroids (OCS) and cytotoxic and/or immunosuppressive agents. However, these treatments can be associated with failure to achieve complete disease remission and significant dose-limiting side effects.^{2,4,7} Moreover, patients receiving standard of care therapy for HES can continue to experience periods of reduced disease control during which

HES-related symptoms worsen and eosinophil counts increase.^{8,9} This loss of control can be incapacitating and may even be life-threatening for some patients.^{3,10}

Mepolizumab is a humanized monoclonal antibody that binds to and neutralizes IL-5, inhibiting IL-5 receptor signaling and blocking eosinophil proliferation, activation, and survival.¹¹⁻¹³ It is approved for the treatment of severe eosinophilic asthma in patients age 6 years and older in multiple regions worldwide, and in the United States for the treatment of eosinophilic granulomatosis with polyangiitis in adults and HES with no identifiable non-hematologic cause in patients age 12 years and older.^{14,15} Prior studies demonstrated that in patients with HES, mepolizumab (750 mg delivered intravenously every 4 or more weeks) permits OCS dose reduction, reduces blood eosinophil counts, and is well-tolerated.^{16,17} A recent phase III, randomized, double-blind, placebo-controlled study (200622)¹⁸ demonstrated that mepolizumab (300 mg administered subcutaneously every 4 weeks) in addition to standard of care therapy reduced flares in patients with uncontrolled FIP1-like-1-platelet-derived growth factor receptor α [*FIP1L1-PDGFR α*]-negative HES compared with placebo, and was associated with a positive benefit–risk profile.

The objective of this open-label extension study, which was conducted after completion of the double-blind study, was to characterize the safety profile and clinical benefit of mepolizumab in this patient population.

METHODS

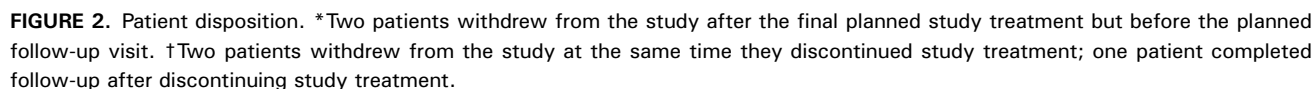
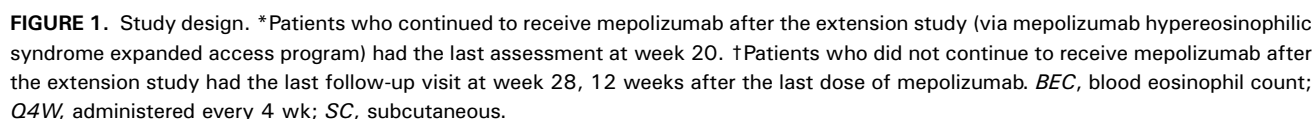
Study design

This was a multicenter, open-label extension (OLE) study (GSK ID 205203; NCT03306043) in patients with HES who completed the double-blind phase III placebo-controlled study (GSK ID 200622; NCT02836496). Patients who previously received placebo or mepolizumab in addition to standard of care therapy in the double-blind study were given the option to participate in the OLE study, during which they received mepolizumab 300 mg subcutaneously every 4 weeks for 20 weeks plus background therapy, with the final dose administered at week 16. After the week 20 clinical visit, patients could choose to continue receiving mepolizumab via an expanded access program (EAP) where available. Those who did not enter the EAP attended an additional follow-up assessment at week 28. Figure 1 illustrates the double-blind and OLE study designs. Investigators and patients were blinded to patient blood eosinophil counts throughout the double-blind study and during weeks 0 to 4 of the OLE study (Figure 1); they were subsequently unblinded until the end of the OLE. During the OLE study, although treating physicians were not specifically instructed to taper background therapies, this was allowed according to clinical judgment, starting 4 weeks after the first dose of mepolizumab.

The double-blind and OLE studies were both conducted in accordance with the International Conference for Harmonization Good Clinical Practice, applicable country-specific requirements, and ethical principles outlined in the Declaration of Helsinki. All patients provided written informed consent before any study-related activities. The studies were approved by the local ethics review boards of the participating sites.

Patients

Key inclusion criteria for the double-blind study were described elsewhere.¹⁸ Briefly, patients age 12 years and older with uncontrolled *FIP1L1-PDGFR α* -negative HES were enrolled. Eligible patients had experienced two or more flares in the previous year



The OLE study enrolled patients who had completed the 32-week treatment period of the double-blind study or had prematurely withdrawn from study treatment but continued to be assessed until week 32. Patients were enrolled from 36 investigational sites in 13 countries (Argentina, Belgium, Brazil, France, Germany, Italy, Poland, Romania, Spain, Mexico, Russia, the United Kingdom, and the United States). Those who had a treatment-related adverse event (AE) during the double-blind study that resulted in permanent study

TABLE I. All adverse effects (AEs), including on-treatment and posttreatment AEs

AEs	Patients, n (%)		
	Mepolizumab 300 mg subcutaneously		
	Previous placebo (n = 52)	Previous mepolizumab (n = 50)	Total (n = 102)
Any AEs	40 (77)	26 (52)	66 (65)
On-treatment AEs	38 (73)	24 (48)	62 (61)
Most frequent* on-treatment AE, by preferred term			
Diarrhea	8 (15)	4 (8)	12 (12)
Pruritus	4 (8)	3 (6)	7 (7)
Headache	4 (8)	2 (4)	6 (6)
Vomiting	6 (12)	0	6 (6)
Arthralgia	4 (8)	1 (2)	5 (5)
Constipation	2 (4)	3 (6)	5 (5)
Nasopharyngitis	2 (4)	3 (6)	5 (5)
Nausea	3 (6)	2 (4)	5 (5)
Sinusitis	2 (4)	3 (6)	5 (5)
Treatment-related† AE, by system organ class	11 (21)	4 (8)	15 (15)
General disorders and administration site conditions	3 (6)	3 (6)	6 (6)
Nervous system disorders	3 (6)	1 (2)	4 (4)
Skin and subcutaneous tissue disorders	4 (8)	0	4 (4)
Infections and infestations	2 (4)	0	2 (2)
Gastrointestinal disorders	1 (2)	0	1 (<1)
Musculoskeletal and connective tissue disorders	1 (2)	0	1 (<1)
Psychiatric disorders	1 (2)	0	1 (<1)
Respiratory, thoracic, and mediastinal disorders	1 (2)	0	1 (<1)
AEs leading to study treatment discontinuation	1 (2)	0	1 (<1)
AEs leading to study withdrawal	1 (2)	0	1 (<1)
Posttreatment‡ AEs, by system organ class	6 (12)	5 (10)	11 (11)
Infections and infestations	2 (4)	2 (4)	4 (4)
Gastrointestinal disorders	3 (6)	0	3 (3)
General disorders and administration site conditions‡	2 (4)	1 (2)	3 (3)
Nervous system disorders	1 (2)	1 (2)	2 (2)
Blood and lymphatic system disorders	0	1 (2)	1 (<1)
Ear and labyrinth disorders	1 (2)	0	1 (<1)
Injury, poisoning, and procedural complications	1 (2)	0	1 (<1)
Musculoskeletal and connective tissue disorders	0	1 (2)	1 (<1)
Respiratory, thoracic, and mediastinal disorders	1 (2)	0	1 (<1)
Fatal AEs	0	0	0

*Reported for ≥5% of patients.

†As assessed by the study investigator.

‡Defined as AEs that started more than 28 days after the last dose of mepolizumab.

TABLE II. All serious adverse events (SAEs) (on-treatment and posttreatment) and adverse events of special interest (AESIs)

SAEs	Patients, n (%)		
	Mepolizumab 300 mg subcutaneously		
	Previous placebo (n = 52)	Previous mepolizumab (n = 50)	Total (n = 102)
Any SAEs	6 (12)	3 (6)	9 (9)
On-treatment SAEs, by preferred term	6 (12)	2 (4)	8 (8)
Bacteremia	0	1 (2)	1 (<1)
<i>Clostridium difficile</i> colitis	0	1 (2)	1 (<1)
Diverticulitis	0	1 (2)	1 (<1)
Gastroenteritis eosinophilic	1 (2)	0	1 (<1)
Gastrointestinal infection	1 (2)	0	1 (<1)
Infective exacerbation of bronchiectasis	1 (2)	0	1 (<1)
Joint dislocation	1 (2)	0	1 (<1)
<i>Mycobacterium abscessus</i> infection	0	1 (2)	1 (<1)
Perihepatic abscess	0	1 (2)	1 (<1)
Peripheral T-cell lymphoma unspecified	1 (2)	0	1 (<1)
Pneumonia	1 (2)	0	1 (<1)
Sinusitis	1 (2)	0	1 (<1)
Treatment-related* on-treatment SAEs, by system organ class and preferred term	1 (2)	0	1 (<1)
Infections and infestations	1 (2)	0	1 (<1)
Sinusitis	1 (2)	0	1 (<1)
SAEs leading to study treatment discontinuation	0	0	0
SAEs leading to study withdrawal	0	0	0
Posttreatment† SAEs, by system organ class and preferred term	0	1 (2)	1 (<1)
Blood and lymphatic system disorders	0	1 (2)	1 (<1)
Hypereosinophilic syndrome‡	0	1 (2)	1 (<1)
Fatal SAEs	0	0	0
AESIs			
Systemic reactions§	3 (6)	0	3 (3)
Anaphylaxis	0	0	0
Allergic (type I hypersensitivity)	2 (4)	0	2 (2)
Other systemic	2 (4)	0	2 (2)
Local injection site reactions§	3 (6)	3 (6)	6 (6)
All infections¶	18 (35)	18 (36)	36 (35)
Potential opportunistic infections#	1 (2)	1 (2)	2 (2)
<i>M abscessus</i> infection	0	1 (2)	1 (1)
Oral herpes	1 (2)	0	1 (1)
Neoplasms¶	3 (6)	1 (2)	4 (4)
Benign breast neoplasm	0	1 (2)	1 (1)
Bowen disease	1 (2)	0	1 (1)
Peripheral T-cell lymphoma, unspecified	1 (2)	0	1 (1)
Uterine leiomyoma	1 (2)	0	1 (1)

(continued)

TABLE II. (Continued)

SAEs	Patients, n (%)		
	Mepolizumab 300 mg subcutaneously		
	Previous placebo (n = 52)	Previous mepolizumab (n = 50)	Total (n = 102)
Malignancies**	2 (4)	0	2 (2)
Bowen disease	1 (2)	0	1 (1)
Peripheral T-cell lymphoma, unspecified	1 (2)	0	1 (1)
Cardiac disorders¶	2 (4)	0	2 (2)
Bundle branch block right	1 (2)	0	1 (1)
Palpitations	1 (2)	0	1 (1)
Serious AESIs			
Infections¶	3 (6)	2 (4)	5 (5)
Cardiac disorders¶	0	0	0
Serious cardiovascular and thromboembolic events**	0	0	0

Serious adverse events were defined as adverse events that were (1) fatal, (2) life-threatening, (3) requiring hospitalization or prolongation of existing hospitalization, (4) resulting in persistent disability or incapacity, (5) a congenital anomaly or birth defect, or (6) other.

*As assessed by the study investigator.

†Defined as SAEs that started more than 28 days after the last dose of mepolizumab.

‡During this event, a blood eosinophil count of 120 cells/μL was recorded. This event was identified as a “HES flare” (verbatim) by the treating investigator.

§Identified by the investigator in case report forms designed for collecting data on systemic reactions and local injection site reactions.

||Considered by the investigator to represent systemic reactions meeting Sampson’s anaphylaxis criteria.

¶Preferred terms within the Infections and Infestations, Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps), and Cardiac Disorders Medical Dictionary for Regulatory Activities (version 22.1) system organ classes.

#Identified based on a published list of pathogens and/or presentations of specific pathogens to be considered as potential opportunistic infections in the setting of biologic therapies.¹⁹

**Identified from prespecified standardized Medical Dictionary for Regulatory Activities (version 22.1) queries.

treatment withdrawal were not eligible for the OLE. Other exclusion criteria were previously outlined for the double-blind study¹⁷ and included current malignancy or malignancy that developed during the double-blind study (excluding cutaneous in situ carcinomas provided they were resected), corrected QT interval greater than 450 ms (or corrected QT interval >480 ms with bundle branch block), and current active liver or biliary disease (except Gilbert syndrome, asymptomatic gallstones, or investigator-assessed chronic liver disease). The safety population included all patients who received one or more dose of mepolizumab, and the pharmacodynamic population included all patients with baseline and one or more post-mepolizumab treatment peripheral blood eosinophil count.

End points and assessments

Primary end points of the OLE study (based on safety) were the proportion of patients with AEs, serious AEs (SAEs), AEs of special interest (AESIs) (previously identified within the mepolizumab clinical development program), and anti-drug antibodies (ADAs). Other safety end points included clinical laboratory tests, vital signs, and electrocardiogram assessments. Exploratory end points (based on efficacy) were the annualized rate of disease flares, change in mean daily OCS dose from weeks 0 to 4 to that at weeks 16 to 20 (in

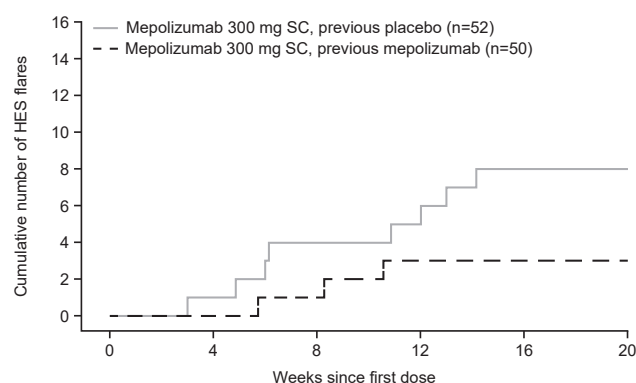


FIGURE 3. Cumulative number of hypereosinophilic syndrome (HES) flares in the open-label extension study (safety population). SC, subcutaneous.

patients receiving OCS during weeks 0 to 4), the proportion of patients receiving OCS during weeks 0 to 4 who achieved a 50% or greater reduction in mean daily OCS dose from weeks 0 to 4 to that at weeks 16 to 20, the proportion of patients achieving a mean daily OCS dose of 7.5 mg or less at weeks 16 to 20 (in patients with an OCS dose of 10 mg/d or greater during weeks 0 to 4 [post hoc analysis]), and change from baseline in blood eosinophil count.

The AEs and SAEs were described as preferred terms and system organ classes (SOCs) according to the Medical Dictionary for Regulatory Activities (MedDRA) (version 22.1; <https://www.meddra.org/>). With regard to AESIs, customized AE/SAE clinical report forms were implemented to collect data regarding systemic reactions and local injection site reactions; malignancies and serious cardiovascular and thromboembolic events were identified from pre-specified standardized MedDRA (version 22.1) queries. Because standardized MedDRA queries for opportunistic infections were unavailable, a published expert opinion was used as a guide for selecting MedDRA preferred terms potentially representing opportunistic infections.¹⁹

Within the context of the OLE study, flares were defined as a worsening of HES-related clinical symptoms and/or an elevated peripheral blood eosinophil count, which required an increase in OCS prednisone-equivalent dose by 10 mg/d or greater for 5 days or more, or an increase in dose or addition of any cytotoxic or immunosuppressive HES therapy plus existing HES therapy that had not been reduced in the past 4 weeks. All study end points were assessed in the total population and stratified by previous placebo or mepolizumab use in the double-blind study.

Sample size and statistical analysis

The sample size of the OLE study was dictated by the number of eligible patients available from the double-blind study. Safety and efficacy end points were measured in the entire OLE study population, with the exception of blood eosinophil counts (three patients were excluded from these analyses owing to missing blood eosinophil counts at baseline). Safety and OCS end points were summarized using descriptive statistics. The rate of flares was analyzed using a negative binomial generalized linear model with a log-link function, including terms for baseline OCS dose from the double-blind study (continuous scale), region, and observed time (as an offset variable). Blood eosinophil counts were log_e-transformed before analysis, with the log transformation for values of 0 GI/L based on a value of

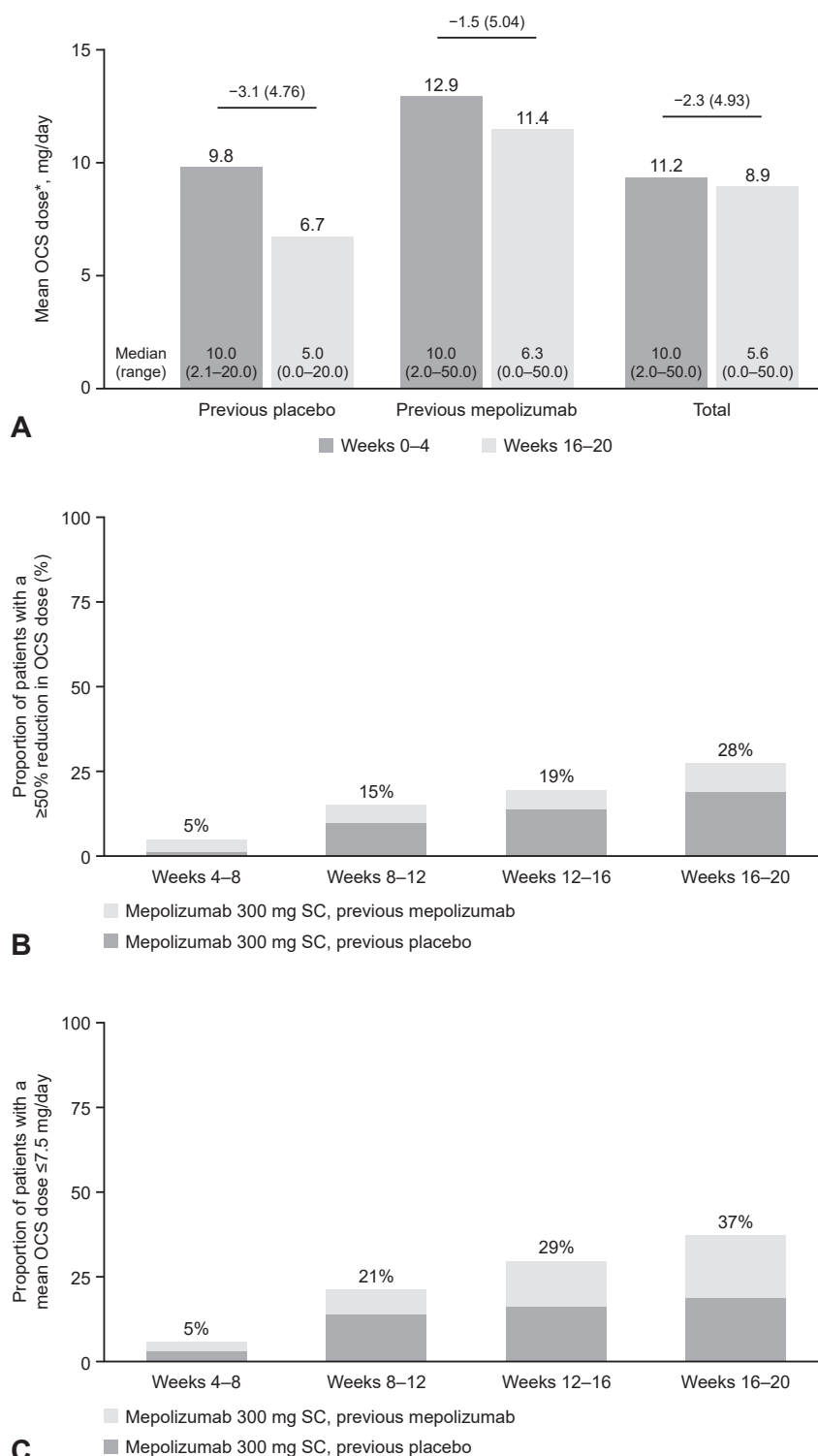


FIGURE 4. Oral corticosteroid (OCS) end points for patients receiving OCS at the start of the open label extension (OLE). **(A)** Mean and median OCS doses at the start and weeks 16 to 20 of the OLE study in addition to mean (SD) change from the start to weeks 16 to 20. **(B)** Proportion of patients who achieved a 50% or greater reduction in OCS dose during the OLE study. **(C)** Proportion of patients with an OCS dose of 10 mg/d or greater at the start of the OLE who achieved a dose of 7.5 mg/d or less during the study. A total of 39 patients (20 in the previous placebo group and 19 in the previous mepolizumab group) had an OCS dose of 10 mg/d or greater at the start (weeks 0–4) of the OLE. All of these patients had available data during weeks 4 to 8 and 38 patients (19 in both the previous placebo and previous mepolizumab group) had available data during weeks 8 to 20. *A total of 73 patients (39 in the previous placebo group and 34 in the previous mepolizumab group) were receiving OCS at the start (weeks 0–4) of the OLE study. All of these patients had available data during weeks 4 to 8 and 72 patients (38 and 34 in the previous placebo and previous mepolizumab groups, respectively) had available data during weeks 8 to 20. SC, subcutaneous.

0.005 GI/L. Absolute and ratio to baseline blood eosinophil counts were summarized by previous treatment group from the double-blind study and visit (geometric mean on the original scale and SD on log_e-transformed data). All analyses were performed using SAS software (version 9.4, SAS Institute Inc, Cary, NC).

RESULTS

Patient population

Of the 104 patients who completed the double-blind study, 98% (n = 102; previous placebo, n = 52; previous mepolizumab, n = 50) were enrolled in the OLE study. This extension study was initiated on November 13, 2017 (first patient, first visit) and completed on December 30, 2019 (last patient, last visit). In total, 98 patients completed the OLE study (96%). Figure 2 shows reasons for patient withdrawals. Patients received a mean 4.6 (SD, 0.42) months of mepolizumab treatment in the OLE study. All 102 enrolled patients were included in the safety population; 99 patients (previous placebo: n = 51; previous mepolizumab: n = 48) were included in the pharmacodynamic population. Patient baseline demographics and clinical characteristics before enrollment in double-blind were reported elsewhere.¹⁷ Mean (SD) patient age was 46.0 (15.54) years; 54% were female. During the double-blind study, HES symptoms reported as most bothersome were breathing problems (56% of patients), skin symptoms (49% of patients), and muscle or joint pain (41% of patients); most bothersome symptoms reported at baseline were similar in both treatment arms of the double-blind study.

Safety

A total of 66 patients (65%) experienced an AE during the OLE study; 62 experienced an on-treatment AE (61%), and 15 experienced an AE that was deemed by the investigator to be related to mepolizumab (15%). The most common on-treatment AEs were diarrhea (12 patients [12%]), pruritus (seven patients [7%]), and headache (six patients [6%]) (Table I). Most frequent on-treatment AEs (according to MedDRA SOC) were infections and infestations (36 patients [35%]), gastrointestinal disorders (22 patients [22%]), and musculoskeletal and connective tissue disorders (18 patients [18%]). The most common infections and infestations included nasopharyngitis (five [patients 5%]), sinusitis, bronchitis, and upper respiratory tract infections (four patients each [4%]); the most common gastrointestinal disorders were diarrhea (12 patients [12%]) and vomiting (six patients [6%]); and the most common musculoskeletal/connective tissue disorder was arthralgia (five patients [5%]). The maximum intensity of reported on-treatment AEs was mild for 18 patients (18%), moderate for 32 (31%), and severe for 12 (12%). Nonserious AEs that were considered to be severe in intensity were fatigue (in two patients) and migraine, abdominal pain, nausea, vomiting, generalized pain, somnolence, asthma, chondropathy, pruritus, and nasopharyngitis (reported in one patient each). The patient with severe generalized pain withdrew from study treatment and from the study; the investigator considered this AE to be related to study treatment but not serious or a systemic reaction. A total of 15 patients (15%) reported AEs that were considered to be related to study treatment (Table I); four experienced injection site reactions and three experienced headaches. All remaining treatment-related AEs were experienced by one patient each. Treatment-related AEs were most

commonly in the category of general disorders and administration site conditions (six patients [6%]) (Table I). Posttreatment AEs, defined as AEs that started more than 28 days after the last dose of mepolizumab, were reported in 11 patients (11%) (Table I). Nasopharyngitis was the only event reported by more than one patient after treatment (n = 2 [2%]).

Nine patients (five male and four female) experienced SAEs (9%) (Table II). Eight patients reported on-treatment SAEs (8%), one of which (sinusitis) was considered by the investigator to be related to study treatment. Five patients (5%) reported on-treatment serious infections, including bacteremia, *Clostridium difficile* colitis, diverticulitis, gastrointestinal infection, infective exacerbation of bronchiectasis, *Mycobacterium abscessus*, perihepatic abscess, pneumonia, and sinusitis. The SAEs that were reported as severe in intensity were worsening of HES symptoms, *M abscessus* infection, eosinophilic gastroenteritis, and peripheral T-cell lymphoma (all reported for one patient each). Two patients experienced one or more SAE during the study (one female patient with pneumonia and gastrointestinal infection; and one male patient with perihepatic abscess, bacteremia, *C difficile* colitis, and *M abscessus* infection). One patient reported a posttreatment SAE of HES (identified as an “HES flare” [verbatim] by the treating investigator) 80 days after the last on-study dose of mepolizumab. No fatal SAEs were reported.

With regard to AESIs for mepolizumab, potential opportunistic infections were reported for two patients (2%) (*M abscessus* infection in one and oral herpes in one) (Table II). Other events of infections were described earlier. In addition, three patients reported events considered by the investigator to represent systemic reactions (3%); all of those were not serious and included allergic (type I hypersensitivity) reactions (rash and urticaria) and other systemic reactions (fatigue and paresthesia). Neoplasms (benign, malignant, and unspecified [including cysts and polyps]) were reported for four patients (4%) (benign breast neoplasm, Bowen disease, peripheral T-cell lymphoma unspecified, and uterine leiomyoma). The nonserious event of Bowen disease and the serious event of peripheral T-cell lymphoma (unspecified) were considered malignancies and were reported as such for two patients (2%) (Table II). The patient with a reported SAE of T-cell lymphoma had circulating phenotypically aberrant (CD3 to CD4⁺) clonal T cells before entering the phase III program and starting treatment with mepolizumab (data not shown). Finally, local injection site reactions occurred in six patients (6%), and cardiac disorders occurred in two patients (2%). No events of anaphylaxis, serious cardiac disorders, or cardiac, vascular, thromboembolic (including ischemic) events were reported (Table II).

One patient (who previously received mepolizumab in the double-blind study) was positive for ADAs with no neutralizing antibodies at baseline, continued to receive mepolizumab, and did not test positive for ADAs at any subsequent time point. No other patients had a positive ADA result at any time after baseline, and no changes of clinical interest in clinical laboratory evaluations, vital signs, or electrocardiogram recordings were observed.

Efficacy

A total of 11 flares were experienced by nine patients (previous placebo: eight events in six patients [two patients experienced two flares, and the remaining four patients experienced one flare

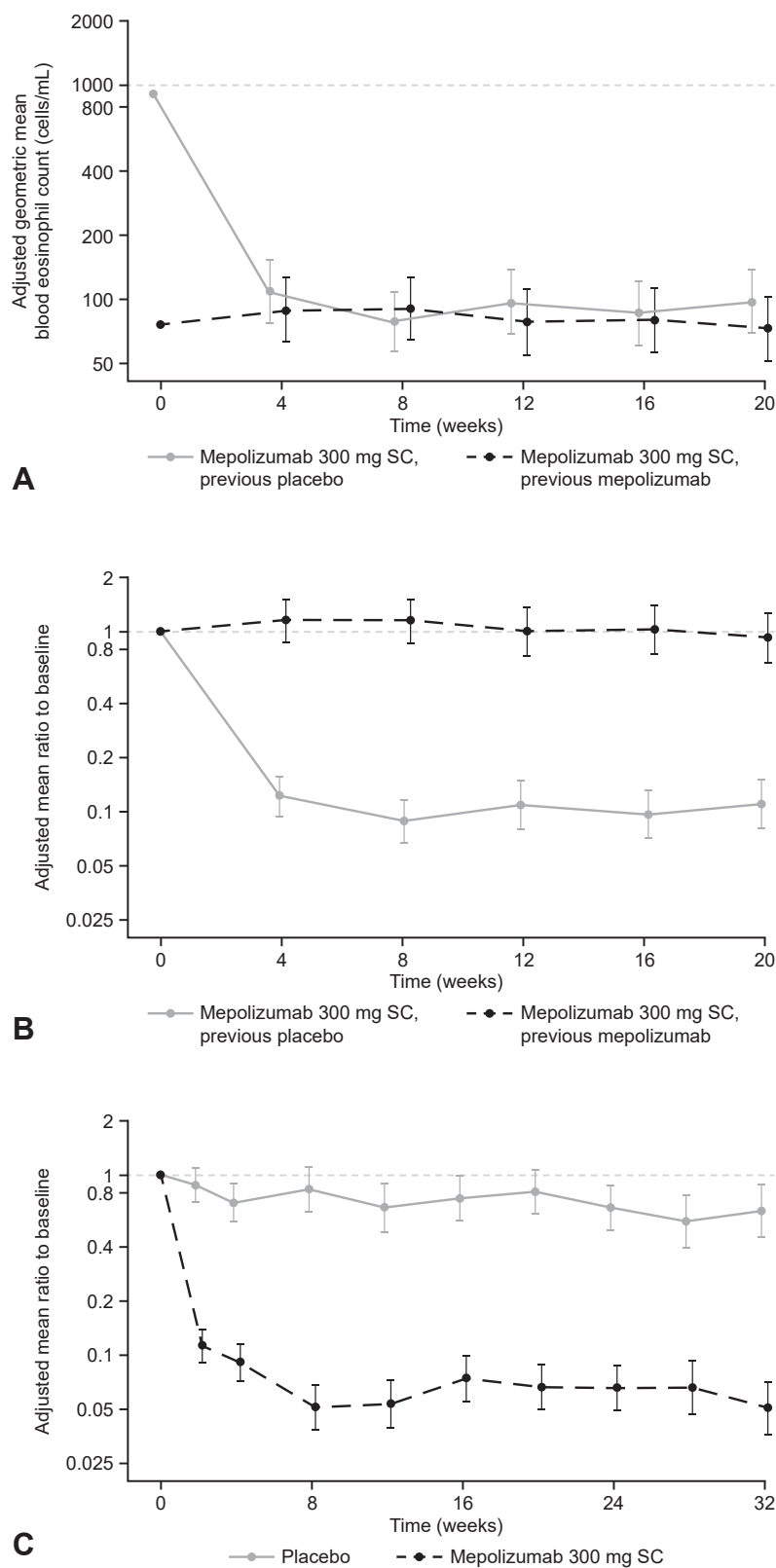


FIGURE 5. Blood eosinophil counts throughout the open-label extension (OLE) study and the initial double-blind study. **(A)** Absolute baseline blood eosinophil counts during the OLE study. **(B, C)** Ratio to baseline blood eosinophil counts during the OLE and double-blind studies, respectively. Vertical bars in all panels represent 95% confidence intervals. SC, subcutaneous.

each]; previous mepolizumab: three events in three patients) (Figure 3) during the OLE 20-week treatment period. All six patients in the previous placebo group who experienced a flare in the OLE study also experienced one or more flare in the preceding double-blind study. Of the three patients in the previous mepolizumab group who experienced a flare, one had experienced a flare in the double-blind study. The annualized rate of flares (95% confidence intervals) across the OLE study was 0.26 (0.13-0.52) events/y overall, 0.37 (0.16-0.86) events/y in the previous placebo group, and 0.14 (0.04-0.49) events/y in the previous mepolizumab group.

A total of 73 patients were receiving OCS at the start of the OLE study, 39 of whom were receiving a mean dose of 10 mg/d or greater. During weeks 16 to 20 of the OLE, OCS data were available for 72 and 38 patients, respectively, in each of these populations. Among patients receiving OCS at the start of the OLE, overall mean (SD) reduction in OCS dose from weeks 0 to 4 to weeks 16 to 20 was -2.3 (4.93) mg/d (-3.1 [4.76] and -1.5 [5.04] mg/d for patients in the previous placebo and previous mepolizumab groups, respectively) (Figure 4, A). Twenty patients achieved a 50% or greater reduction in mean daily dose (28%; 14 and six patients in the previous placebo and previous mepolizumab groups, respectively) (Figure 4, B). Among patients receiving 10 mg/d or greater OCS at the start of the OLE, 14 (37%) were receiving 7.5 mg/d or less by weeks 16 to 20 (seven in the previous placebo group and seven in the previous mepolizumab group) (Figure 4, C). Median daily OCS doses were the same for patients previously receiving placebo and mepolizumab in the double-blind study (10.0 mg/d for both groups) (Figure 4, C).

For patients who previously received placebo in the double-blind study, geometric mean (SD log) blood eosinophil counts were reduced from 910 (1.142) cells/ μ L at week 0 to between 70 (1.148) and 110 (1.262) cells/ μ L across the 20-week OLE study treatment period (Figure 5, A). This corresponded to an 88% adjusted mean reduction in blood eosinophil count at week 4, which was sustained through week 20 (89% reduction) (Figure 5, B). For patients who were treated with mepolizumab in the double-blind study (Figure 5, C), the geometric mean (SD log) blood eosinophil count was 80 (1.349) cells/ μ L at the baseline of the OLE study and remained at a similar count until week 20.

DISCUSSION

This 20-week OLE study included 102 of 104 patients with *FIP1L1-PDGFR*A-negative HES who completed a previous phase III randomized, placebo-controlled trial of mepolizumab. In the current study, no new safety signals were observed with mepolizumab 300 mg subcutaneous treatment. Moreover, the efficacy and pharmacodynamic results demonstrate that mepolizumab continued to control HES flares, reduced OCS dependence, and maintained reductions in blood eosinophil counts for patients who previously received mepolizumab. For patients who previously received placebo, mepolizumab reduced HES flare rates, OCS use, and blood eosinophil counts from weeks 0 to 4 to weeks 16 to 20 of the extension study. This study excluded patients with the *FIP1L1-PDGFR*A fusion gene, because tyrosine kinase inhibitors are currently available as an effective targeted treatment option for *FIP1L1-PDGFR*A-positive patients.²⁰

Our safety findings support those of a previous randomized controlled study of mepolizumab in patients with HES, which

demonstrated similar frequencies of AEs and SAEs in patients receiving intravenous mepolizumab 750 mg or placebo for 32 weeks.¹⁶ They are also consistent with AEs identified in a long-term open-label safety study of up to 5-years mepolizumab (intravenous 750 mg) treatment in patients with HES.¹⁷ Although herpes zoster is an opportunistic infection associated with the use of immune-targeting biologics,¹⁹ no herpes zoster infections or reactivations were observed in this study.

Disease flares can be unpredictable, incapacitating, and even life-threatening for many patients with HES, often necessitating treatment escalation.^{3,21} Therefore, reducing the occurrence of disease flares is an important goal of HES treatment. In this study, patients in the previous placebo group experienced a mean annualized rate of 0.37 flares/y, versus 1.46 events/y during the double-blind study and 2.7 events in the prior year. Moreover, there was no evidence of a loss of mepolizumab efficacy: Patients in the previous mepolizumab group experienced a mean annualized rate of 0.14 flares/y in the OLE study and 0.50 flares/y in the double-blind study. However, a formal head-to-head comparison of flare rates during the double-blind and OLE studies was not possible owing to the different definitions for disease flares employed in the two studies. Treatment blinding in the double-blind study meant that investigator-determined HES flares could not be guided by blood eosinophil counts. Therefore, for safety reasons, we also used a second definition for flares (blood eosinophil counts above an individualized prespecified threshold that required two or more courses of blinded rescue OCS intervention). In contrast, the definition of a flare used in the OLE study was more reflective of real-world practice, in which investigators use both symptoms and blood eosinophil counts to evaluate disease control.

Because long-term OCS use is associated with predictable adverse effects,²² reducing OCS dependence is a key goal of nonsteroidal HES therapies. Although this was not a formal OCS-sparing trial (treating physicians could taper OCS as of week 4 but were not specifically instructed to do so), we observed a reduction in OCS use among patients who were receiving OCS at the start of the OLE study. Within the short (20-week) study period, mean OCS doses were reduced from 11.2 to 8.9 mg/d and 28% of patients were able to reduce OCS use by at least 50%. Moreover, 37% of those receiving 10 mg/d or greater at the start of the OLE achieved an OCS dose of 7.5 mg/d or less by study end. Many expert clinicians recommend the use of other therapies to support OCS tapering in patients requiring greater than 10 mg/d (prednisolone equivalent).² Another key goal of HES treatments is to reduce blood eosinophil counts. It is thought that lower blood eosinophil counts are associated with reduced tissue damage in patients with HES.^{8,23} In this study, blood eosinophil counts remained suppressed for patients who had previously received mepolizumab, and were reduced by approximately 90% from baseline for those who had previously received placebo.

Possibly owing to the encouraging safety and efficacy results observed with mepolizumab, we noted high adherence to mepolizumab treatment across the phase III study and the extension study. Overall, 91% of 108 patients enrolled in the initial double-blind study completed both the 32-week phase III study and the 20-week OLE; most opted to continue receiving mepolizumab in the subsequent EAP.

Several limitations to this open-label study must be considered when interpreting the results. First, the absence of a placebo

control group prevents the analysis of treatment differences. Second, a direct comparison of flare rates across studies was not possible owing to differing patients' background therapies (including blinded OCS administered during the double-blind study) and per-protocol definitions of a flare between the initial phase III study and the open-label extension. Third, the short treatment duration (20 weeks) and the small number of patients who experienced a flare during the OLE study preclude a meaningful analysis of long-term disease control and background therapy use with mepolizumab. Fourth, tissue histology was not assessed and mortality events were absent in this study; therefore, the impact of mepolizumab on HES disease progression, mortality, and objective measures of tissue or organ damage during flares will need to be addressed in future long-term studies. Finally, this open-label extension study was designed to assess the safety and efficacy only of 4-weekly 300 mg subcutaneous mepolizumab. Future studies will be useful to determine the safety and efficacy of alternative mepolizumab dosing regimens among patients with different disease phenotypes and characteristics.

The results of this extension study reinforce that long-term mepolizumab treatment is associated with a positive benefit–risk profile and continues to control flare rates, allows for reductions in OCS use, and reduces blood eosinophil counts in a population of patients with *FIP1L1-PDGFR*A-negative HES who experience flares. These results provide further evidence of the clinical benefit of subcutaneous mepolizumab 300mg for patients with HES.

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