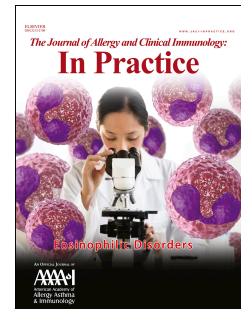


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Safety and efficacy of mepolizumab in hypereosinophilic syndrome: an open-label extension study

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Abstract

Background: A double-blind, placebo-controlled Phase III study (200622) showed that mepolizumab reduces disease flares for patients with uncontrolled *FIP1L1-PDGFR*A-negative hypereosinophilic syndrome (HES) and ≥ 2 flares in the previous year.

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

Results: Of 104 patients who completed the double-blind study, 98% (previous placebo n=52; previous mepolizumab n=50) enrolled in the OLE. Overall, 66 (65%) patients reported adverse events (AEs); 15 (15%) reported treatment-related AEs and 9 (9%) reported serious AEs. 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/year, respectively. Of 72 patients receiving OCS during Weeks 0–4, 20 (28%; previous placebo, n=14; previous mepolizumab, n=6) achieved $\geq 50\%$ reductions in mean daily dose during Weeks 16–20. At Week 20, BEC was reduced by 89% in patients previously receiving placebo and remained reduced for those previously receiving mepolizumab.

Conclusion: 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 *FIP1L1-PDGFR*A-negative HES.

Highlights:**1. 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 *FIP1L1-PDGFR*A-negative hypereosinophilic syndrome (HES), with a positive benefit:risk profile.

2. 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*A-negative HES. Moreover, mepolizumab continued to control flares and blood eosinophil counts over 52 weeks of continuous treatment.

3. How does this study impact current management guidelines?

The findings from this open-label extension study provide further evidence that patients with *FIP1L1-PDGFR*A-negative HES are likely to benefit from treatment with mepolizumab and may be able to reduce their oral corticosteroid use.

Keywords: hypereosinophilic syndrome, mepolizumab, anti-IL-5, safety, efficacy, flare, oral corticosteroid.

Abbreviations

ADA, anti-drug antibodies; AE, adverse event; AESI, adverse event of special interest; CVT, cardiovascular and thromboembolic; EAP, expanded access program; ECG, electrocardiogram; *FIP1L1-PDGFR*A, FIP1-like-1-platelet-derived growth factor receptor α ; HES, hypereosinophilic syndrome; IL, interleukin; IV, intravenous; OCS, oral corticosteroids; OLE, open-label extension; SAE, serious adverse event; SC, subcutaneous.

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 is not secondary to 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 are often dependent 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, in order to reverse and prevent further eosinophil-mediated end-organ damage and to

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 their HES-related symptoms worsen, and/or their 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 interleukin (IL)-5, thus 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 ≥ 6 years of age in multiple regions worldwide, and in the USA for the treatment of eosinophilic granulomatosis with polyangiitis in adults and HES without an identifiable non-hematologic cause in patients ≥ 12 years of age.^{14,15} Prior studies have demonstrated that in patients with HES, mepolizumab (750 mg delivered intravenously [IV] every ≥ 4 weeks) permits OCS dose reduction, reduces blood eosinophil counts, and is well-tolerated.^{16,17} A recent Phase III, randomized, double-blinded, placebo-controlled study (200622) demonstrated that mepolizumab (300 mg administered subcutaneously [SC] 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.¹⁸

The objective of this open-label extension study, conducted after completion of the double-blind study, was to further 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 SC every 4 weeks for 20 weeks plus background therapy, with the final dose administered at Week 16. After their 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. The double-

blind and OLE study designs are summarized in **Figure 1**. Investigators and patients were blinded to patient blood eosinophil counts throughout the double-blind study and during Weeks 0–4 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 as per clinical judgement, starting 4 weeks after the first dose of mepolizumab.

The double-blind and OLE studies were both conducted in accordance with 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 prior to any study-related activities. The studies were approved by local ethics review boards of the participating sites.

Patients

Key inclusion criteria for the double-blind study have been previously described.¹⁸ Briefly, patients ≥ 12 years of age with uncontrolled *FIP1L1-PDGFR*A-negative HES were enrolled. Eligible patients had experienced ≥ 2 flares in the previous year (defined as a worsening of HES-related clinical symptoms or a peripheral blood eosinophil count requiring an escalation in therapy; ≥ 1 flare had to be unrelated to a decrease in HES therapy in the preceding 4 weeks) and a peripheral blood eosinophil count ≥ 1000 cells/ μ L at screening. Patients were also receiving stable doses of HES therapy (including, but not limited to, OCS, immunosuppressive, and/or cytotoxic therapy) ≥ 4 weeks before randomization.

The OLE study enrolled patients who had completed the 32-week treatment period of the double-blind study, or who prematurely withdrew 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, UK and USA). Those who had a treatment-related adverse event (AE) during the double-blind study that resulted in permanent study treatment withdrawal were not eligible for the OLE. Other exclusion criteria have been previously outlined for the double-blind study,¹⁷ and included: current malignancy or malignancy that developed during the double-blind study (excluding cutaneous in situ carcinomas provided they were resected); QTc > 450 msec (or QTc > 480 msec with bundle branch block); current active liver or biliary disease (except Gilbert's syndrome, asymptomatic gallstones or investigator-assessed chronic liver disease). The safety population included all patients who received ≥ 1 dose of mepolizumab and the pharmacodynamic population included all patients with baseline and ≥ 1 post-mepolizumab treatment peripheral blood eosinophil count.

Endpoints and assessments

The primary endpoints 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 endpoints included clinical laboratory tests, vital signs, and electrocardiogram (ECG) assessments. Exploratory endpoints (based on efficacy) were: the annualized rate of disease flares, change in mean daily OCS dose from Weeks 0–4 at Weeks 16–20 (in patients receiving OCS during Weeks 0–4), the proportion of patients receiving OCS during Weeks 0–4 who achieved a $\geq 50\%$ reduction in mean daily OCS dose from Weeks 0–4 to Weeks 16–20, the proportion of patients achieving a mean daily OCS dose ≤ 7.5 mg at Weeks 16–20 (in patients with an OCS dose ≥ 10 mg/day during Weeks 0–4 [post hoc analysis]), and change from baseline in blood eosinophil count.

AEs and SAEs were described as preferred terms and system organ classes (SOCs), as per the Medical Dictionary for Regulatory Activities (MedDRA; V22.1). With regards to AESIs, customized AE/SAE clinical report forms were implemented to collect data on systemic reactions and local injection site reactions; malignancies and serious CVT events were identified from prespecified standardized MedDRA (V22.1) queries. Since standardized MedDRA queries for opportunistic infections were not available, a published expert opinion was used as a guide for selecting MedDRA preferred terms potentially representing opportunistic infections.¹⁹

In 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/day for ≥ 5 days or 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. All study endpoints 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 endpoints were measured in the entire OLE study population, with the exception of blood eosinophil counts (3 patients were excluded from these analyses owing to missing blood eosinophil counts at baseline). Safety and OCS endpoints 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 prior to analysis, with the log transformation for values of 0 GI/L based on a value of 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 standard deviation on log_e-transformed data). All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

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 13 November 2017 (first patient, first visit) and completed on 30 December 2019 (last patient, last visit). In total, 98 (96%) patients completed the OLE study; reasons for patient withdrawals are shown in **Figure 2**. Patients received a mean 4.6 (standard deviation [SD]: 0.42) months of mepolizumab treatment in the OLE study. All 102 of the enrolled patients were included in the safety population and 99 patients (previous placebo: n=51; previous mepolizumab: n=48) were included in the pharmacodynamic population. Patient baseline demographics and clinical characteristics prior to enrollment in double-blind have been reported previously.¹⁷ The mean (SD) patient age was 46.0 (15.54) years and 54% were female. During the double-blind study, the 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 (65%) patients experienced an AE during the OLE study; 62 (61%) experienced an on-treatment AE, and 15 (15%) patients experienced an AE that was deemed related to mepolizumab by the investigator. The most common on-treatment AEs were diarrhea (in 12 [12%] patients), pruritus (in 7 [7%] patients), and headache (in 6 [6%] patients) (**Table I**). On-treatment AEs in the following categories (according to MedDRA SOCs) were reported most frequently: infections and infestations (reported in 36 [35%] patients), gastrointestinal disorders (in 22 [22%] patients), and musculoskeletal and connective tissue disorders (in 18 [18%] patients). The most common infections and infestations included nasopharyngitis (in 5 [5%] patients), sinusitis, bronchitis, and upper respiratory tract infections (each in 4 [4%] patients); the most common gastrointestinal disorders were diarrhea (in 12 [12%] patients) and vomiting (in 6 [6%] patients), and the most common

musculoskeletal/connective tissue disorder was arthralgia (in 5 [5%] patients). The maximum intensity of reported on-treatment AEs was mild for 18 (18%) patients, moderate for 32 (31%) patients, and severe for 12 (12%) patients. The non-serious AEs that were considered severe in intensity were fatigue (in 2 patients), and migraine, abdominal pain, nausea, vomiting, generalized pain, somnolence, asthma, chondropathy, pruritus, and nasopharyngitis (reported in 1 patient each). The one 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 (15%) patients reported AEs that were considered related to study treatment (**Table I**); 4 patients experienced injection site reactions and 3 patients experienced headaches, with all remaining treatment-related AEs each experienced by 1 patient. Treatment-related AEs were most commonly in the category of 'general disorders and administration site conditions' (6 [6%] patients; **Table I**). Post-treatment AEs, defined as AEs that started more than 28 days after the last dose of mepolizumab, were reported in 11 (11%) patients (**Table I**); nasopharyngitis was the only event reported by >1 patient (n=2 [2%]) post-treatment.

In total, 9 (9%) patients experienced SAEs, outlined in **Table II**. Among these, 5 patients were male and 4 were female. Eight (8%) patients reported on-treatment SAEs, 1 of which (sinusitis) was considered by the investigator to be related to study treatment. Five (5%) patients 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, mycobacterium abscessus infection, eosinophilic gastroenteritis, and peripheral T-cell lymphoma (all reported for 1 patient each). Two patients experienced >1 SAE during the study (one female patient with pneumonia and gastrointestinal infection; one male patient with perihepatic abscess, bacteremia, clostridium difficile colitis, and mycobacterium abscessus infection). One patient reported a post-treatment SAE of HES (identified as a "HES flare" [verbatim] by the treating investigator), 80 days after their last on-study dose of mepolizumab. No fatal SAEs were reported.

With regards to AESIs for mepolizumab, potential opportunistic infections were reported for 2 (2%) patients (mycobacterium abscessus infection in 1 patient and oral herpes in 1 patient; **Table II**); other events of infections have been described above. In addition, 3 (3%) patients reported events that were considered by the investigator to represent systemic reactions, all of which were non-serious and included allergic (type I hypersensitivity) reactions (rash, urticaria) and other systemic reactions (fatigue, paresthesia). Neoplasms (benign, malignant and 'unspecified' [including cysts and

polyps]) were reported for 4 (4%) patients (benign breast neoplasm, Bowen's disease, peripheral T-cell lymphoma unspecified, and uterine leiomyoma); the nonserious event of Bowen's disease and the serious event of peripheral T-cell lymphoma (unspecified) were considered malignancies and were reported as such for 2 (2%) patients (**Table II**). Of note, the patient with a reported SAE of T-cell lymphoma had circulating phenotypically aberrant (CD3-CD4+) clonal T cells prior to entering the Phase III program and starting treatment with mepolizumab (data not shown). Finally, local injection site reactions occurred in 6 (6%) patients and cardiac disorders occurred in 2 (2%) patients. No events of anaphylaxis, serious cardiac disorders, or cardiac, vascular, thromboembolic (including ischemic) events were reported (**Table II**).

One patient (previously receiving 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 timepoint. No other patients had a positive ADA result at any time post-baseline and no changes of clinical interest in clinical laboratory evaluations, vital signs, or ECG recordings were observed.

Efficacy

A total of 11 flares were experienced by 9 patients (previous placebo: 8 events in 6 patients [2 patients experienced 2 flares, the remaining 4 patients experienced 1 flare each]; previous mepolizumab: 3 events in 3 patients; **Figure 3**) during the OLE 20-week treatment period. All 6 of the patients in the previous placebo group who experienced a flare in the OLE study also experienced ≥ 1 flare in the preceding double-blind study; of the 3 patients in the previous mepolizumab group who experienced a flare, 1 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/year overall, 0.37 (0.16, 0.86) in the previous placebo group and 0.14 (0.04, 0.49) in the previous mepolizumab group.

A total of 73 patients were receiving OCS at the start of the OLE study, of whom 39 were receiving a mean dose ≥ 10 mg/day; during Weeks 16–20 of the OLE, OCS data were available for 72 and 38 patients in each of these populations, respectively. Among the patients receiving OCS at the start of the OLE, the overall mean (SD) reduction in OCS dose from Weeks 0–4 to Weeks 16–20 was -2.3 (4.93) mg/day (-3.1 [4.76] and -1.5 [5.04] mg/day for patients in the previous placebo and previous mepolizumab groups, respectively; **Figure 4A**); 20 (28%) patients achieved a $\geq 50\%$ reduction in mean daily dose (14 and 6 patients in the previous placebo and previous mepolizumab groups, respectively; **Figure 4B**). Among those patients receiving ≥ 10 mg/day OCS at the start of the OLE, 14 (37%) were receiving ≤ 7.5 mg/day by Weeks 16–20 (7 patients in the previous placebo group and 7

in the previous mepolizumab group; **Figure 4C**). Of note, median daily OCS doses were the same for patients previously receiving placebo and mepolizumab in the double-blind study (10.0 mg/day for both groups; **Figure 4C**).

For patients who previously received placebo in the double-blind study, geometric mean (standard deviation [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 5A**). This corresponded to an 88% adjusted mean reduction in blood eosinophil count at Week 4, which was sustained through to Week 20 (89% reduction; **Figure 5B**). For those patients treated with mepolizumab in the double-blind study (**Figure 5C**), the geometric mean (SD log) blood eosinophil count was 80 (1.349) cells/ μ L at baseline of the OLE study and remained at a similar count until Week 20.

Discussion

This 20-week OLE study included 102 of the 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 SC 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 those patients who previously received placebo, mepolizumab reduced HES flare rates, OCS use, and blood eosinophil counts from Weeks 0–4 to Weeks 16–20 of the extension study. This study excluded patients with the *FIP1L1-PDGFR*A fusion gene, given that 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 mepolizumab 750 mg IV or placebo for 32 weeks.¹⁶ They are also consistent with the AEs identified in a long-term open-label safety study of up to 5 years' mepolizumab (750 mg IV) treatment in patients with HES.¹⁷ Despite herpes zoster being 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, and often necessitate treatment escalation.^{3,21} Reducing the occurrence of disease flares is

therefore an important goal of HES treatment. In this study, patients in the previous placebo group experienced a mean annualized rate of 0.37 flares/year, versus 1.46 events/year 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/year in the OLE study and 0.50 flares/year in the double-blind study. However, it is important to note that 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, a second definition for flares was also utilized (blood eosinophil counts above an individualized prespecified threshold that required ≥ 2 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, where investigators use both symptoms and blood eosinophil counts to evaluate disease control.

Since long-term OCS use is associated with predictable adverse effects,²² reducing OCS-dependence is a key goal of non-steroidal 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/day and 28% of patients were able to reduce their OCS use by at least 50%. Moreover, 37% of those receiving ≥ 10 mg/day at the start of the OLE achieved an OCS dose ≤ 7.5 mg/day by study end. Of note, many expert clinicians recommend the use of other therapies to support OCS tapering in patients requiring >10 mg/day (prednisolone equivalent).² Another key goal of HES treatments is to reduce blood eosinophil counts. Indeed, it is thought that lower blood eosinophil counts are likely to lead to be 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 the 108 patients enrolled in the initial double-blind study completed both the 32-week Phase III study and the 20-week OLE, with a majority opting to continue receiving mepolizumab in the subsequent EAP.

There are several limitations to this open-label study that 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 the 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; the impact of mepolizumab on HES disease progression, mortality and objective measures of tissue/organ damage during flares will therefore need to be addressed in future long-term studies. Finally, this open label extension study was designed to assess the safety and efficacy of 4-weekly 300 mg subcutaneous mepolizumab only; future studies will be useful to determine the safety and efficacy of alternative mepolizumab dosing regimens among patients with different disease phenotypes/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 mepolizumab 300 mg SC for patients with HES.

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Data availability statement

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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Tables

Table I. Summary of all AEs, including on-treatment and post-treatment AEs.

	n (%) patients		
	Mepolizumab 300 mg SC		
	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 AEs, 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[†] AEs, by SOC	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)
Post-treatment* AEs, by SOC	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.

AE, adverse event; SC, subcutaneous; SOC, system organ class.

Table II. Summary of all SAEs (on-treatment and post-treatment) and AESIs.

	n (%) patients		
	Mepolizumab 300 mg SC		
	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)
Clostridium difficile 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)
Mycobacterium abscessus 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 SOC 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
Post-treatment† SAEs, by SOC 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)
Mycobacterium abscessus 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's disease	1 (2)	0	1 (1)
Peripheral T-cell lymphoma, unspecified	1 (2)	0	1 (1)
Uterine leiomyoma	1 (2)	0	1 (1)
Malignancies††	2 (4)	0	2 (2)
Bowen's 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 CVT events ^{††}	0	0	0
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SAEs were defined as adverse events that were either: a) fatal, b) life-threatening, c) requiring hospitalization or prolongation of existing hospitalization, d) resulting in persistent disability/incapacity e) a congenital anomaly/birth defect, f) 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/ μ L 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’ MedDRA (V22.1) SOC; ^{††}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 therapies¹⁹; ^{‡‡}identified from prespecified standardized MedDRA (V22.1) queries.

AE, adverse event; AESI, adverse event of special interest; CVT, cardiovascular and thromboembolic; HES, hypereosinophilic syndrome; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SC, subcutaneous; SOC, system organ class.

Figure Legends

Figure 1. Study design

*Patients who continued to receive mepolizumab after the extension study (via mepolizumab HES EAP) had their last assessment on Week 20; [†]patients who did not continue to receive mepolizumab after the extension study had their last follow-up visit at Week 28, 12 weeks after their last dose of mepolizumab.

BEC, blood eosinophil count; EAP, expanded access program; HES, hypereosinophilic syndrome; Q4W, administered every 4 weeks; SC, subcutaneous.

Figure 2. Patient disposition

*Two patients withdrew from the study after the final planned study treatment but before the planned follow-up visit; [†]2 patients withdrew from the study at the same time they discontinued study treatment; 1 patient completed follow-up after discontinuing study treatment.

Figure 3. Cumulative number of HES flares in the OLE study (safety population)

HES, hypereosinophilic syndrome; OLE, open-label extension; SC, subcutaneous.

Figure 4. Summary of OCS endpoints in patients receiving OCS at the start* of the OLE

Panel A shows mean and median OCS doses at the start* and Weeks 16–20 of the OLE study in addition to mean (SD) change from the start* to Weeks 16–20, Panel B shows the proportion of patients who achieved a $\geq 50\%$ reduction in OCS dose during the OLE study, and Panel C shows the proportion of patients with an OCS dose ≥ 10 mg/day at the start[†] of the OLE who achieved a dose ≤ 7.5 mg/day during the study.

*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 4–8 and 72 patients (38 and 34 in the previous placebo and previous mepolizumab groups, respectively) had available data during Weeks 8–20; [†]39 patients (20 in the previous placebo group and 19 in the previous mepolizumab group) had an OCS dose ≥ 10 mg/day at the start (Weeks 0–4) of the OLE: all of these patients had available data during Weeks 4–8 and 38 patients (19 in both the previous placebo and previous mepolizumab group) had available data during Weeks 8–20.

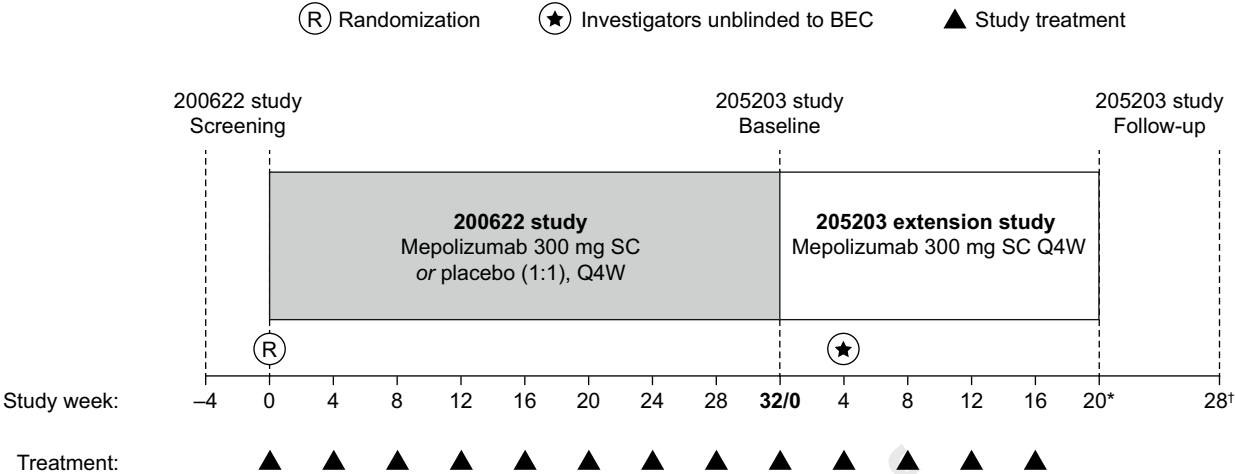
OCS, oral corticosteroids; OLE, open label extension; SC, subcutaneous.

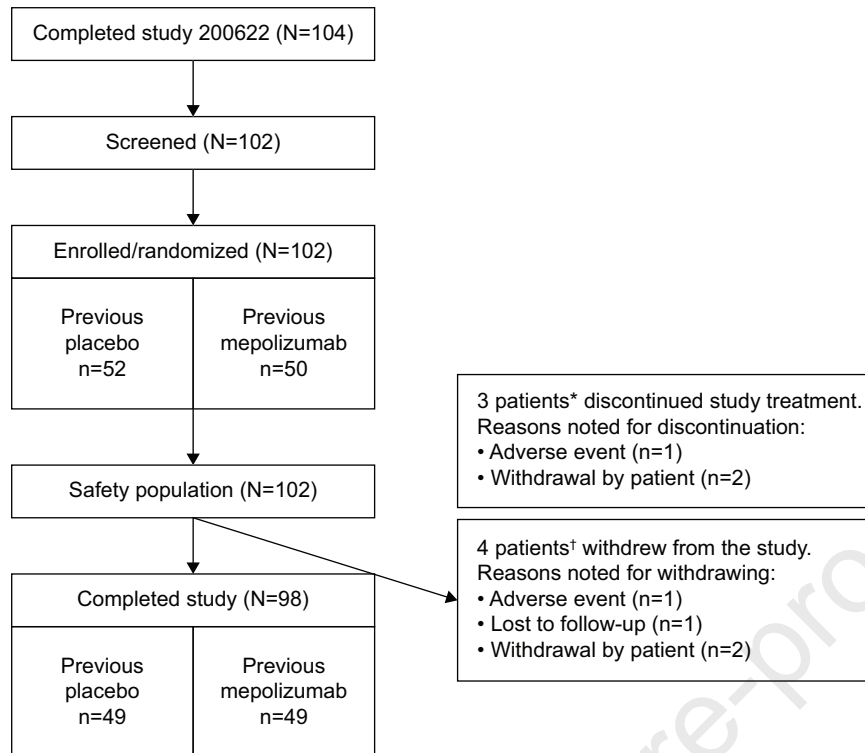
Figure 5. Blood eosinophil counts throughout the open-label extension study and the initial double-blind study

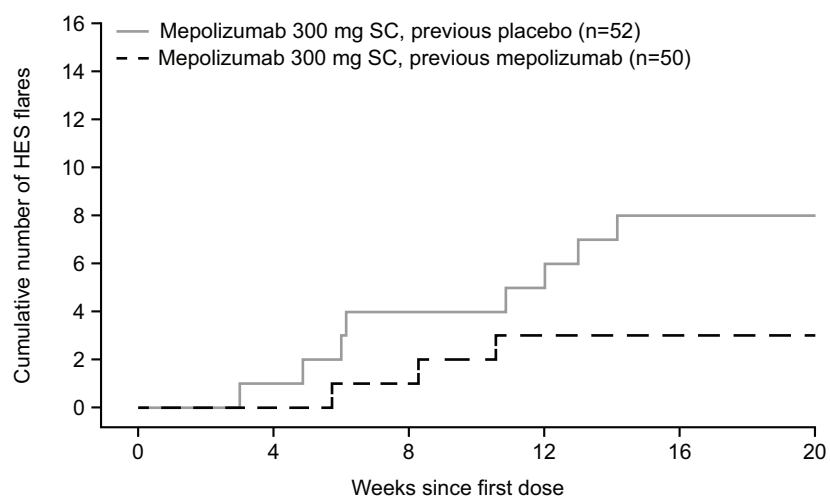
Panel A shows absolute baseline blood eosinophil counts during the OLE study. Panels B and C show ratio to baseline blood eosinophil counts during the OLE and double-blind studies, respectively.

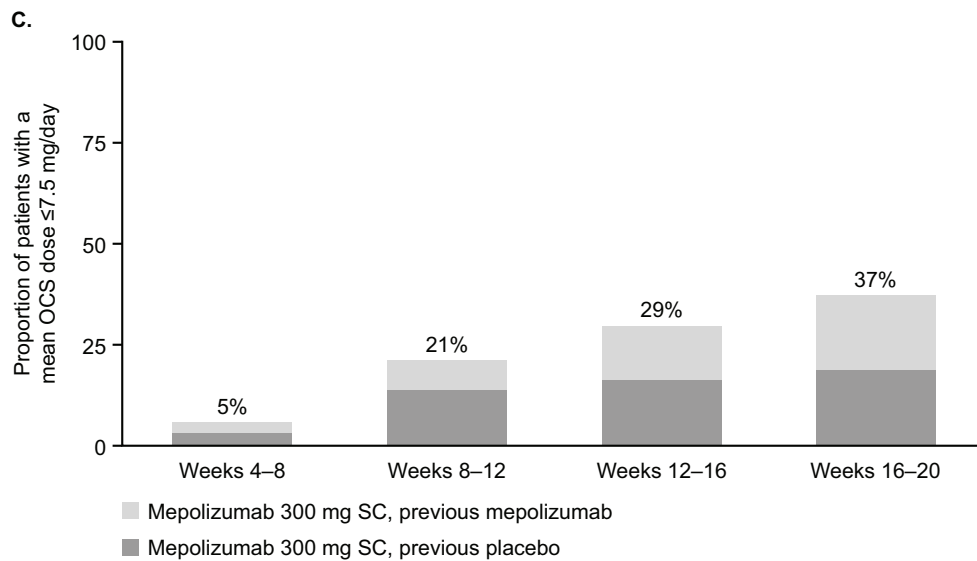
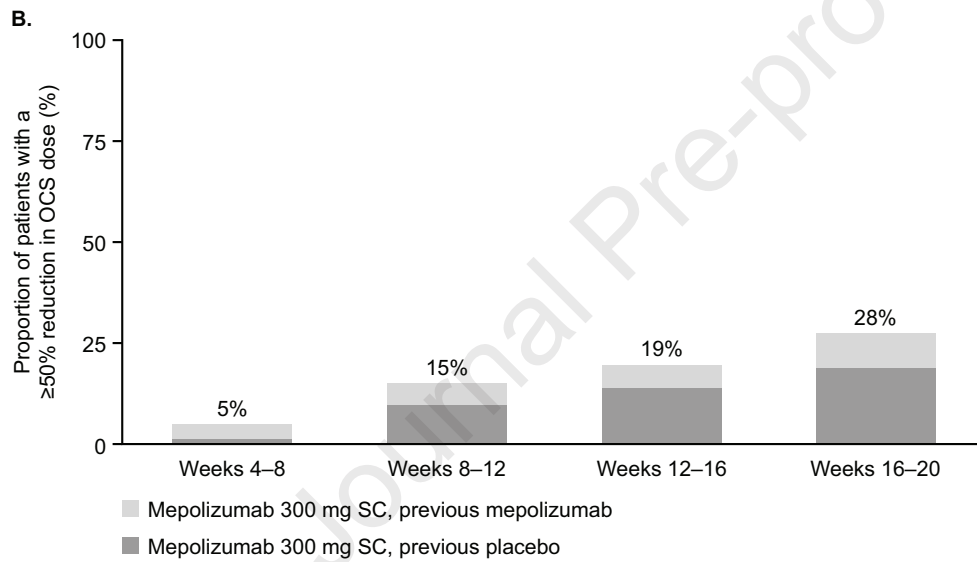
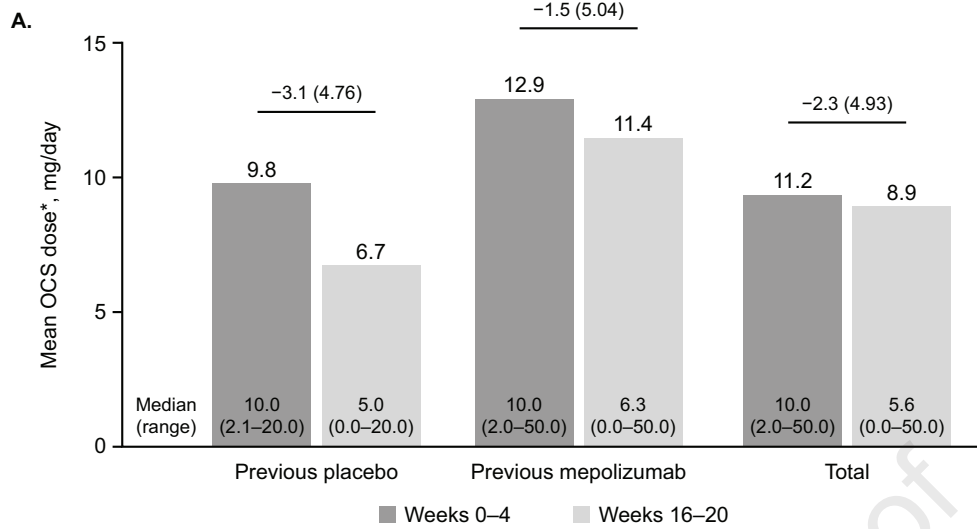
Vertical bars in all panels represent 95% CI.

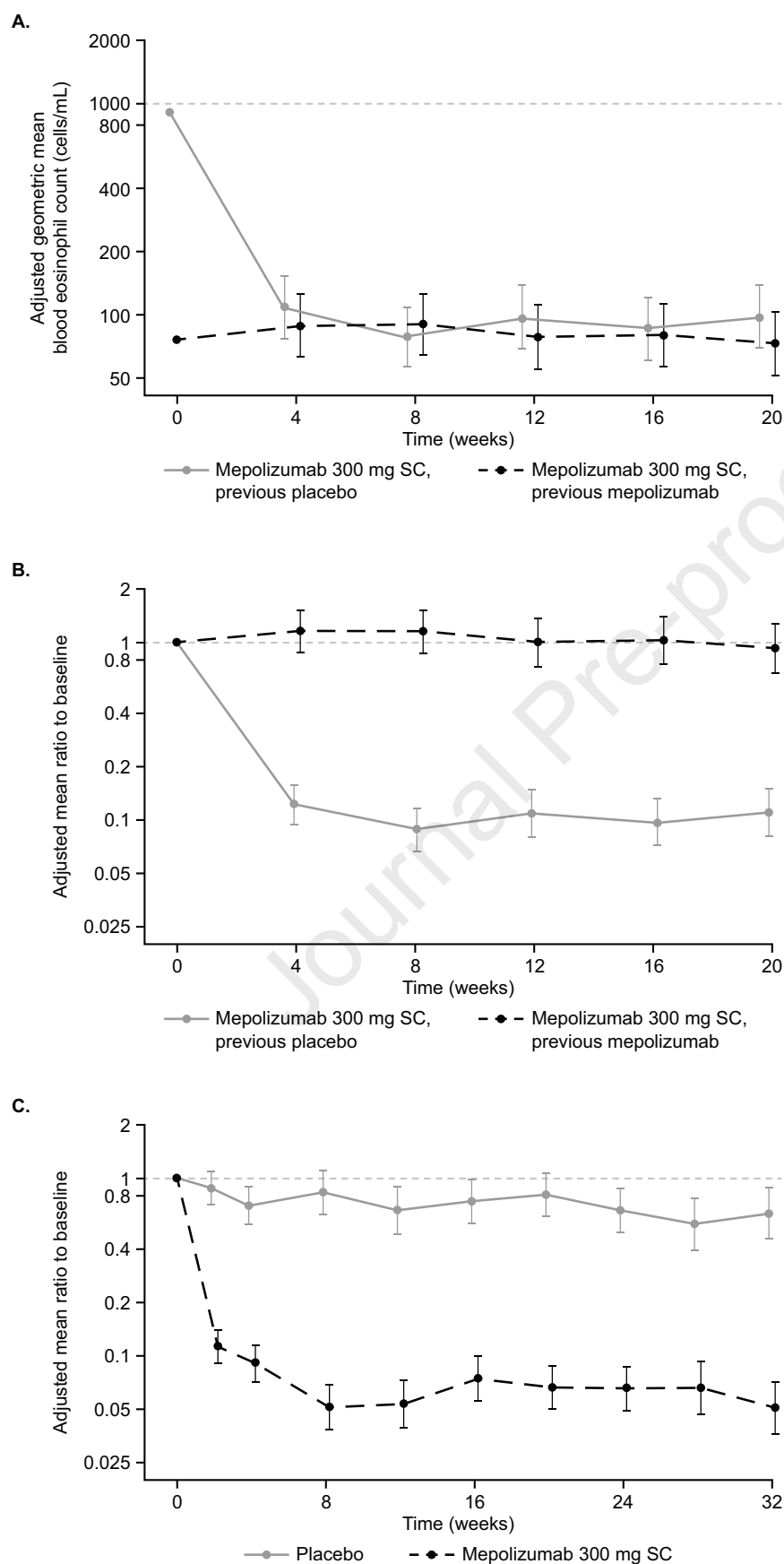
CI, confidence interval; SC, subcutaneous.











Online Repository

Safety and efficacy of mepolizumab in hypereosinophilic syndrome: an open-label extension study

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