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Mepolizumab reduces hypereosinophilic syndrome flares irrespective of blood eosinophil count and IL-5

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1 **Abstract** [Word count: 250/250]

2 **Background:** Mepolizumab, an anti-interleukin [IL]-5 antibody, reduces disease flares
3 in patients with hypereosinophilic syndrome (HES); factors predicting treatment
4 response are unknown.

5 **Objective:** To assess mepolizumab efficacy by baseline blood eosinophil count (BEC)
6 and serum IL-5 level in patients with HES.

7 **Methods:** This post hoc analysis used data from the Phase III study assessing
8 mepolizumab in patients with HES (NCT02836496). Patients ≥ 12 years old, with HES
9 for ≥ 6 months, ≥ 2 flares in previous year, and BEC ≥ 1000 cells/ μ L at screening were
10 randomized (1:1) to 4-weekly subcutaneous mepolizumab (300mg) or placebo, plus
11 baseline HES therapy, for 32 weeks. The proportion of patients experiencing ≥ 1 flare
12 (Week 32), annualized flare rate, and proportion of patients with change from
13 baseline in Brief Fatigue Inventory (BFI) item 3 (Week 32), were analyzed by baseline
14 BEC ($<1500/\geq 1500$ – $<2500/\geq 2500$ cells/ μ L); flare outcomes were assessed by baseline
15 serum IL-5 ($<7.81/\geq 7.81$ pg/mL).

16 **Results:** Across baseline BEC subgroups, mepolizumab reduced the proportion of
17 patients experiencing ≥ 1 flare by 63–90% and flare rate by 58–84% (treatment-by-
18 eosinophil interaction $P=0.76$ and $P=0.90$, respectively); patients had improved BFI
19 item 3 score with mepolizumab versus placebo (cells/ μ L: <1500 : 54% vs 37%; ≥ 1500 –
20 <2500 : 47% vs 31%; ≥ 2500 : 61% vs 0%; treatment-by-eosinophil interaction $P=0.42$).
21 Most patients had undetectable baseline serum IL-5 levels; among these,

22 mepolizumab versus placebo reduced the proportion of patients with ≥ 1 flare (77%)
23 and flare rate (67%).

24 **Conclusion:** Mepolizumab was efficacious in the patients with HES studied,
25 irrespective of baseline BEC. Undetectable IL-5 levels should not preclude
26 mepolizumab treatment.

27 **Clinical trial registry:** ClinicalTrials.gov; NCT02836496

28 **Highlights**

29 *What is already known about this topic? (words: 32/≤35)*

30 Mepolizumab is the first biologic therapy to be approved for the treatment of HES.

31 Previous studies demonstrated that mepolizumab reduced disease flares and

32 improved fatigue severity versus placebo in patients with HES.

33 *What does this article add to our knowledge? (words: 33/≤35)*

34 Our analysis shows that mepolizumab is associated with reductions in disease flares

35 and fatigue severity irrespective of baseline blood eosinophil count and also showed

36 efficacy in patients with an undetectable serum IL-5 level.

37 *How does this study impact current management guidelines? (words: 31/≤35)*

38 Patients with HES are likely to achieve clinical benefit with mepolizumab treatment,

39 independent of baseline blood eosinophil count; patients should be considered for

40 mepolizumab treatment irrespective of detectable serum IL-5 levels.

41 **Keywords:** baseline blood eosinophil count, flare, fatigue, IL-5, hypereosinophilic

42 syndrome, mepolizumab.

43 **Abbreviations**

44 *BFI* *Brief Fatigue Inventory*

45 *HES* *Hypereosinophilic syndrome*

46 *IL* *Interleukin*

47 *IS* *Cytotoxic and/or immunosuppressive therapies*

- 48 *OCS* *Oral corticosteroids*
- 49 *OLE* *Open-label extension*
- 50

Introduction

Hypereosinophilic syndrome (HES) is a rare and debilitating multisystem disorder characterized by elevated eosinophil counts in the peripheral blood and tissues and eosinophil-mediated organ damage.¹ Sustained elevated eosinophil counts can affect all organ systems and as such the clinical presentation of patients with HES is heterogenous,^{1,2} although skin, lung, cardiovascular and gastrointestinal involvement are the most common manifestations.^{1,3} Ultimately, the extent of organ system dysfunction is linked to the severity of clinical manifestations, therefore, the aim of treatment is to prevent, and, if possible, reverse organ damage to improve patient outcome.^{2,4,5} With the exception of patients with imatinib-sensitive HES variants, current standard of care treatment for HES includes oral corticosteroids (OCS) and cytotoxic and/or immunosuppressant therapies (IS).² However, these have variable clinical efficacy and are associated with substantial side effects.^{3,6}

Mepolizumab is a humanized monoclonal antibody that binds to and inactivates interleukin-5 (IL-5), thereby blocking the proliferation, activation, and survival of eosinophils.⁷ Mepolizumab is approved for the treatment of severe eosinophilic asthma, and eosinophilic granulomatosis with polyangiitis in multiple regions worldwide, and recently has also been approved for use in patients with HES and chronic rhinosinusitis with nasal polyps.⁸⁻¹⁰ The approval of mepolizumab for the treatment of HES was based on the findings from the double-blind, Phase III 200622 study (NCT02836496).¹¹ This study and the open-label extension (OLE) study (NCT03306043) in patients with HES demonstrated that mepolizumab treatment reduced the frequency of disease flares, fatigue severity, OCS use, and blood eosinophil count, versus placebo, respectively, with no new safety signals identified,^{11,12} which was consistent with an earlier preliminary report.¹³

74 A relationship between mepolizumab efficacy and baseline blood eosinophil count has been
75 established for eosinophil-driven diseases such as severe eosinophilic asthma.^{10, 11} However,
76 the impact of baseline blood eosinophil count or detectable serum IL-5 level on
77 mepolizumab clinical treatment responses in HES is unknown. We therefore hypothesized
78 that relative elevations in baseline blood eosinophil count or serum IL-5 level may lead to
79 patients with HES deriving greater clinical benefit from mepolizumab treatment than those
80 patients with a lower baseline blood eosinophil count or lower serum IL-5 level. The
81 objective of this post hoc analysis of data from the 200622 study was to assess the impact of
82 baseline blood eosinophil count and serum IL-5 level on reductions in flares and fatigue
83 observed with mepolizumab treatment.

Methods

Study design and patients

This was a post hoc analysis of data from the 200622 study, which was a randomized, placebo-controlled, double-blind, parallel-group, multicenter, Phase III trial (NCT02836496). Full details of this study have been reported previously.¹¹ Briefly, after screening, patients were randomized (1:1) to receive subcutaneous injections of mepolizumab 300 mg or placebo every 4 weeks for 32 weeks in addition to their existing HES therapy. The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and applicable country-specific regulatory requirements. All patients provided written informed consent. Full patient eligibility criteria have been reported previously;¹¹ in brief, patients were ≥ 12 years of age at screening and had a diagnosis of HES ≥ 6 months before screening. Patients with the *FIP1L1-PDGFR*A rearrangement were excluded. A HES diagnosis was based on organ system involvement and/or dysfunction that could be directly related to a blood eosinophil count >1500 cells/ μ L on ≥ 2 occasions, and/or tissue eosinophilia, without a discernible secondary cause. Patients had to have stable HES therapy for ≥ 4 weeks before the baseline visit, had ≥ 2 flares within the past 12 months and a blood eosinophil count ≥ 1000 cells/ μ L at screening.

Post hoc analysis outcomes

The endpoints assessed during this post hoc analysis were the proportion of patients who experienced ≥ 1 flare during the 32-week study period, the annualized rate of flares, and the proportions of patients with increases, no change and reductions from baseline in Brief

Fatigue Inventory (BFI) item 3 (worst level of fatigue in past 24 hours) at Week 32 (primary and secondary endpoints in the 200622 study, respectively).¹¹ BFI item 3 was recorded using an eDiary (BFI range 0–10; higher score indicates worse fatigue). The minimal clinically important difference in BFI item 3 for patients with HES was not determined. In the 200622 study, 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 IS HES therapy or b) receipt of ≥ 2 courses of blinded OCS during the treatment period.¹¹ This post hoc analysis included flares meeting either definition.

Baseline serum total IL-5 categories (undetectable [<7.81] or ≥ 7.81 pg/mL) were analyzed by baseline oral corticosteroid use (yes/no) post hoc. All endpoints were analyzed by pre-specified baseline (i.e. the randomization visit) blood eosinophil count categories (<900 , ≥ 900 – <1500 , ≥ 1500 – <2200 , ≥ 2200 cells/ μ L). For this post hoc analysis, baseline blood eosinophil count was categorized into: <1500 , ≥ 1500 – <2500 and ≥ 2500 cells/ μ L, on the basis of their clinical relevance and to improve the statistical power for each subgroup. Baseline blood eosinophil counts were measured at the randomization visit, up to 4 weeks after screening (note: patients received stable HES therapy for ≥ 4 weeks prior to baseline and throughout the 32-week treatment period). Flare endpoints were also assessed according to serum IL-5 at baseline, based on the limit of detection for serum IL-5 (undetectable [<7.81] or ≥ 7.81 pg/mL). At baseline, Week 32, and in the event of a flare, serum samples were collected for measurement of IL-5 levels by enzyme-linked immunosorbent assay; free and total IL-5 were measured with a detection range of 3.91–500 pg/mL and 7.81–500 pg/mL, respectively.

129 *Statistical analysis*

130 Full details of the statistical analysis for the 200622 study have been published previously.¹¹
131 Briefly, the proportion of patients with a flare was analyzed using a logistic regression
132 analysis adjusted for treatment and baseline OCS dose. Patients who withdrew prematurely
133 from the study were included in the analysis as having a flare. The annualized rate of flares
134 was analyzed using a negative binomial regression model with covariates of baseline OCS
135 dose, region, baseline blood eosinophil count, and observed time (as an offset variable).
136 Change from baseline in fatigue severity at Week 32 was summarized and the median
137 change in BFI item 3 was presented. Patients with missing data were included in this analysis
138 with the largest (ie, worst) value observed for any patient. Change from baseline in fatigue
139 severity at Week 32 (BFI item 3) was analyzed using mixed model repeated measures with
140 covariates of baseline OCS dose, baseline blood eosinophil count, region, treatment, and
141 visit, plus interaction terms for visit-by-baseline, visit-by-treatment group, and visit-by-
142 baseline blood eosinophil count. All analyses were performed using SAS software, version
143 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient baseline demographics and clinical characteristics

Baseline demographics and clinical characteristics of the 108 patients who participated in the 200622 study have been previously reported.¹¹ Within the total population, 56 patients had a blood eosinophil count <1500 cells/ μ L, 31 had $\geq$ 1500–2500 cells/ μ L, and 21 had $\geq$ 2500 cells/ μ L at baseline; patient demographics and clinical characteristics according to baseline blood eosinophil count subgroups are shown in **Table 1**. Patients with a baseline blood eosinophil count $\geq$ 1500 cells/ μ L (ie, $\geq$ 1500–<2500 and $\geq$ 2500 cells/ μ L) were numerically older, had a slightly longer duration of HES, a higher number of historical flares, and were receiving a higher daily OCS dose than patients with a blood eosinophil count <1500 cells/ μ L. Furthermore, a greater proportion of patients with a baseline blood eosinophil count $\geq$ 1500 cells/ μ L (ie, $\geq$ 1500–<2500 and $\geq$ 2500 cells/ μ L) reported skin symptoms as a most bothersome symptom, and fewer patients reported nasal or sinus symptoms than patients with a blood eosinophil count <1500 cells/ μ L.

Impact of mepolizumab by baseline blood eosinophil count

The odds of a patient experiencing $\geq$ 1 flare was reduced by at least 63% with mepolizumab versus placebo, across all baseline blood eosinophil count subgroups; patients with $\geq$ 2500 cells/ μ L experienced the greatest reduction (**Figure 1A**). However, modeling analyses indicated no significant interaction between baseline blood eosinophil count and mepolizumab efficacy ($P = 0.76$; **Figure 1C**). Likewise, mepolizumab treatment was also associated with at least a 58% reduction in the annualized rate of flares versus placebo, across all baseline blood eosinophil count subgroups. Patients with $\geq$ 2500 cells/ μ L experienced the greatest reduction in the annualized rate of flares with mepolizumab versus

placebo (**Figure 1B**), although the modeling analysis indicated no significant interaction between baseline blood eosinophil count and mepolizumab treatment ($P = 0.897$; **Figure 1D**).

In all baseline blood eosinophil count subgroups, a higher proportion of patients treated with mepolizumab versus placebo demonstrated an improvement from baseline in fatigue severity (BFI item 3) score at Week 32 (**Figures 2A, 2B, and 2C**). However, the modeling analysis indicated no significant interaction between baseline blood eosinophil count and mepolizumab treatment ($P = 0.423$; **Figure 2D**). Of note, in patients receiving placebo, a greater proportion with a baseline blood eosinophil count ≥ 1500 – <2500 cells/ μL (62%) or ≥ 2500 cells/ μL (63%) had a worsening of BFI item 3 score at Week 32 compared with placebo-treated patients who had a baseline blood eosinophil count <1500 cells/ μL (29%; **Figures 2A, 2B, and 2C**).

Impact of mepolizumab by baseline serum IL-5 level

The majority of patients (79.6%, $n=86$) had an undetectable baseline serum IL-5 level (≤ 7.81 pg/mL; **Figure E1** in Online Repository), irrespective of whether they were treated with OCS at baseline (with OCS use: 77%, no OCS use: 87%; see **Table E2** in Online Repository). The blood eosinophil count in patients receiving placebo was similar across serum IL-5 level thresholds and for the duration of the study (**Figure 3**). The baseline blood eosinophil count for patients with an undetectable serum IL-5 level (<7.81 pg/mL) was similar between mepolizumab and placebo groups (1360 cells/ μL ; **Figure 3A**), whereas the baseline blood eosinophil count in patients with a detectable baseline serum IL-5 level (≥ 7.81 pg/mL) was higher in those receiving mepolizumab than placebo (2190 cells/ μL vs 1330 cells/ μL ; **Figure 3B**). In patients receiving mepolizumab, the blood eosinophil count decreased after baseline

and remained low for the duration of the study (≤ 250 cells/ μ L), irrespective of baseline serum IL-5 threshold (**Figure 3**).

For patients with an undetectable baseline serum IL-5 level (< 7.81 pg/mL), mepolizumab treatment was associated with a 77% reduction in the proportion of patients experiencing ≥ 1 flare versus placebo; no treatment effect was observed in patients with a detectable serum IL-5 level (≥ 7.81 pg/mL; **Figure 4**); however, the number of patients in this subgroup was small ($n=22$). Mepolizumab treatment was also associated with a 67% reduction in the annualized rate of flares in patients with an undetectable IL-5 level versus placebo; in patients with a detectable IL-5 level, a 54% numerical reduction in the annualized rate of flares was observed with mepolizumab versus placebo, although the confidence intervals were large (**Figure 4**).

Discussion

Blood eosinophil counts are a well-established biomarker for predicting the response to mepolizumab treatment in patients with severe eosinophilic asthma.^{14,15} However, for rare and heterogeneous diseases such as HES, determining the impact of a particular biomarker on the likelihood of a treatment response is more challenging, in part owing to the lower prevalence, heterogeneity in the underlying pathogenic mechanisms, and variable clinical presentation of the disease.¹⁶ The current analysis demonstrated that mepolizumab reduced the proportion of patients experiencing ≥ 1 flare during the 32-week treatment period, reduced the annualized rate of flares and reduced fatigue severity versus placebo, irrespective of baseline blood eosinophil count and in patients with undetectable serum IL-5 at baseline. Furthermore, our modeling analysis did not suggest a treatment effect with increasing blood eosinophil count, either for the proportion of patients with at least one flare, the annualized flare rate, or fatigue severity, although it is worth noting that the small sample size may not have been powered to drive statistical results. These data highlight the consistent clinical benefit with mepolizumab in patients with HES across a range of baseline blood eosinophil counts and for patients with undetectable serum IL-5.

While evidence of elevated blood and/or tissue eosinophil counts is critical for a diagnosis of HES, the available evidence is limited to support a sole role for eosinophil counts in determining severity of disease.^{17,18} Our data showed that patients with a baseline blood eosinophil count ≥ 1500 cells/ μ L were typically older, had a slightly longer duration of HES, a higher number of historical flares, and were receiving a higher daily OCS dose than patients with a blood eosinophil count < 1500 cells/ μ L, suggestive of more severe disease in patients with a higher blood eosinophil count. As such, the finding that mepolizumab was associated

with improvements in the number and rate of flares and fatigue across all blood eosinophil count subgroups indicates the benefit of mepolizumab, including in patients with more severe disease. Notably, these analyses were also performed in baseline blood eosinophil count subgroups with thresholds (based on quartiles) that were pre-specified in the original study analysis plan (see **Table E1** in Online Repository). The outcomes in these subgroups were in line with the findings from this post hoc analysis, indicating mepolizumab was efficacious across all baseline blood eosinophil groups tested. In keeping with these findings, the modeling analyses did not support a treatment effect with increasing baseline blood eosinophil count, which further supports the consistent effect of mepolizumab across the HES patient population, irrespective of blood eosinophil count.

Given mepolizumab's mechanism of action, we also assessed the impact of baseline serum IL-5 level on the number and rate of flares with mepolizumab treatment. These results did not indicate a change in treatment effect for mepolizumab with an increasing baseline serum IL-5 level for any of the outcomes measured in the small number of patients with detectable IL-5. However, we did demonstrate that mepolizumab was efficacious in patients with an undetectable baseline serum IL-5 level. A lack of association between biologic treatment responses and the associated target cytokine has been reported in other eosinophilic diseases as well as in other diseases with an underlying inflammatory pathophysiology.^{19,20} Our results are also consistent with a previous report assessing mepolizumab efficacy in patients with HES, in which most patients had an undetectable serum IL-5 level at baseline, although, clinical response parameters were not assessed.¹³ In contrast, a retrospective observational study of patients treated with intravenous mepolizumab (750 mg), demonstrated that clinical responses correlated with pre-treatment serum IL-5 levels.²¹ It is important to note that the inclusion criteria for that study were

more stringent compared with those employed in our study as patients with life-threatening HES with at least three prior failed conventional HES therapies were eligible for inclusion.²¹ Nonetheless, our results are of significant clinical relevance as they suggest that a detectable serum IL-5 level is not a prerequisite for treatment with mepolizumab and that patients with HES are likely to experience clinical benefit with mepolizumab even if they have undetectable levels of serum IL-5.

The limitations of the parent study have been reported previously.¹¹ For the current analysis, the post hoc nature is a key limitation, and in particular, the small patient numbers included in each baseline blood eosinophil count subgroup and in the detectable baseline serum IL-5 level subgroup. Power calculations for this study have been reported previously,¹¹ estimating a sample size of 120 patients was required to detect an absolute reduction of 38% in the proportion of patients experiencing a flare during the study. As we reported data from 56, 31, and 21 patients with a baseline blood eosinophil count <1500 cells/ μ L, $\geq$ 1500–<2500 cells/ μ L, and $\geq$ 2500 cells/ μ L, respectively, the significance testing for this analysis was underpowered. In addition, most patients had an undetectable baseline serum IL-5 level, limiting the interpretation of the impact of baseline serum IL-5 level on mepolizumab efficacy. It is also worth noting that 72% of patients in the study were using OCS in the 12 months prior to the study and 21% were using cytotoxic/immunosuppressive therapy in this period. OCS use has been reported to reduce blood eosinophil counts,²² therefore the decision to stratify our analyses by baseline blood eosinophil count may have been confounded by background OCS use. Furthermore, as corticosteroids can repress the transcription of numerous cytokines, including IL-5,^{23,24} prior treatment may have impacted the IL-5 levels seen at baseline, although the post hoc analyses did not support this (see **Table E2** in Online Repository). While our findings are valid for this patient population,

272 further investigation into the utility of baseline blood eosinophil count in predicting
273 treatment responses to mepolizumab in the heterogeneous patient population attending
274 clinical practice is required. Nonetheless, this analysis provides clinically relevant
275 information on the effect of mepolizumab in patients with HES across a range of baseline
276 blood eosinophil counts and in patients with an undetectable baseline serum IL-5 level.

277 In conclusion, this analysis indicates that patients with HES are likely to achieve clinically
278 important reductions in disease flares and improvements in fatigue with mepolizumab
279 treatment, irrespective of baseline blood eosinophil count. Our findings suggest that
280 baseline blood eosinophil count does not significantly influence treatment outcomes with
281 mepolizumab and mepolizumab is also of benefit to patients with an undetectable serum IL-
282 5 level at treatment initiation.

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Data availability statement

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

Author's contributions

FR, GJG, JS, EM and SWY were involved in the conception or design of the analysis; MER, FR, SF, GJG, JS, SWY, EM and NK were involved in the data analysis or interpretation; MER, FR, SF and GJG contributed to the acquisition of data. All authors reviewed and revised the manuscript critically for important intellectual content, agreed to submit to the current journal, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Figures and tables

Figure 1. Proportion of patients experiencing flares (A and C) and annualized rate of flares (B and D) during the 32-week treatment period by baseline blood eosinophil count.

For panels C and D, the shaded area represents 95% CIs; the reference line represents the result for the overall population.

CI, confidence interval; HES, hypereosinophilic syndrome; SC, subcutaneous.

371 **Figure 2.** Change from baseline in BFI item 3 score (worst level of fatigue in past 24 hours) at
372 Week 32 by baseline blood eosinophil count and treatment arm.

373 For panel D, the shaded area represents 95% CIs; the reference line represents the result for
374 the overall population.

375 CI, confidence interval; BFI, Brief Fatigue Inventory; HES, hypereosinophilic syndrome; SC,
376 subcutaneous.

377 **Figure 3.** Blood eosinophil count over time stratified by baseline serum IL-5 level <7.81
378 pg/mL (A) and ≥ 7.81 pg/mL (B).

379 Error bars represent SD logs. Data were log transformed prior to analysis; where a result of
380 zero was recorded, this was replaced with 0.005 prior to log transformation.

381 IL, interleukin; SC, subcutaneous; SD, standard deviation.

382 **Figure 4.** Proportion of patients experiencing a flare and annualized rate of flares during the 32-week treatment period by baseline serum IL-5 level.

383 Odds/rate ratio <1 indicates a lower proportion of patients with ≥ 1 flare or a lower flare rate with mepolizumab versus placebo.

384 CI, confidence interval; HES, hypereosinophilic syndrome; IL, interleukin; SC, subcutaneous.

Table 1. Patient baseline demographics and characteristics by baseline blood eosinophil

count.

	Total N=108	Baseline blood eosinophil count (cells/ μ L)		
		<1500 n=56	$\geq$ 1500–<2500 n=31	$\geq$ 2500 n=21
Age, years, mean (SD)	46.0 (15.78)	43.2 (16.91)	47.3 (15.68)	51.5 (11.00)
Female, n (%)	57 (53)	29 (52)	17 (55)	11 (52)
BMI, kg/m², mean (SD)	26.29 (5.883)	25.39 (4.445)	27.35 (8.074)	27.12 (5.316)
Duration of HES, years, mean (SD)	5.55 (6.691)	5.38 (7.627)	5.71 (4.346)	5.79 (7.144)
Number of historical flares*, mean (SD)	2.7 (1.2)	2.6 (1.1)	2.7 (1.0)	2.9 (1.4)
Most bothersome HES symptoms[†], n (%)				
Abdominal pain or bloating	40 (37)	21 (38)	11 (35)	8 (38)
Breathing symptoms	60 (56)	33 (59)	15 (48)	12 (57)
Chills or sweats	15 (14)	7 (13)	5 (16)	3 (14)
Muscle or joint pain	44 (41)	24 (43)	10 (32)	10 (48)
Nasal or sinus symptoms	41 (38)	26 (46)	8 (26)	7 (33)
Skin symptoms	53 (49)	22 (39)	19 (61)	12 (57)
Baseline HES therapy, n (%)				
Any	99 (92)	51 (91)	27 (87)	21 (100)
OCS	78 (72)	41 (73)	21 (68)	16 (76)
$\leq$ 20 mg/day [‡]	72 (67)	38 (68)	19 (61)	15 (71)
>20 mg/day [‡]	6 (6)	3 (5)	2 (6)	1 (5)
Cytotoxic/Immunosuppressive therapy	23 (21)	11 (20)	7 (23)	5 (24)
Other	41 (38)	22 (39)	12 (39)	7 (33)
Not taking OCS or cytotoxic/immunosuppressive therapy	25 (23)	13 (23)	9 (29)	3 (14)
OCS[‡] daily dose, mg, mean (SD)	8.0 (9.17)	7.2 (8.64)	8.6 (10.48)	9.4 (8.69)
BFI score, mean (SD)	4.57 (2.614)	4.64 (2.662)	4.96 (2.575)	3.78 (2.497)
Blood eosinophil count, geo. mean (SD log) [range]	1400 (0.832) [30–18350]	800 (0.677) [30–1460]	1900 (0.143) [1510–2460]	3980 (0.508) [2520–18350]

*In the 12 months prior to screening; [†]as reported by patients; at baseline/randomization,

patients reported up to 3 HES-related symptoms that they considered most bothersome;

[‡]prednisone or equivalent.

BFI, Brief Fatigue Inventory; BMI, body mass index; HES, hypereosinophilic syndrome; geo,

geometric; OCS, oral corticosteroid; SD, standard deviation.

1 **Table E1.** Pre-specified baseline blood eosinophil subgroup analysis.

	Baseline blood eosinophil category (cells/ μ L)			
	<900	≥ 900 —<1500	≥ 1500 —<2200	≥ 2200
	n=26	n=30	n=25	n=27
Patients with ≥ 1 flare or who withdrew from the study by Week 32				
Odds ratio (95% CI)	0.11 (0.01, 1.01)	0.89 (0.18, 4.42)	0.13 (0.02, 0.91)	0.16 (0.03, 0.98)
Rate of flares by Week 32				
Rate ratio (95% CI)	0.43 (0.17, 1.12)	0.48 (0.13, 1.80)	0.22 (0.05, 1.02)	0.24 (0.06, 0.95)

2 Odds ratio calculated using a logistic regression analysis adjusted for baseline OCS dose and region. Rate ratios were calculated using a negative binomial

3 regression adjusted for baseline OCS dose. Odds/Rate ratio <1 indicates lower rate of HES flares with mepolizumab compared with placebo.

4 CI, confidence interval; HES, hypereosinophilic syndrome; OCS, oral corticosteroid.

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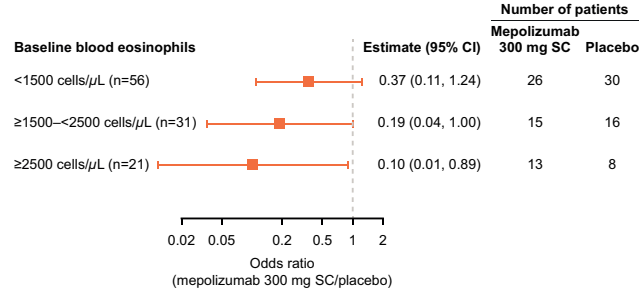
6 **Table E2.** Post hoc baseline OCS use by baseline serum total IL-5 category analysis.

	Baseline serum total IL-5 category (pg/mL)	
	<7.81 n=86	≥7.81 n=22
Baseline OCS use, n (%)		
Yes	60 (70)	18 (82)
No	26 (30)	4 (18)

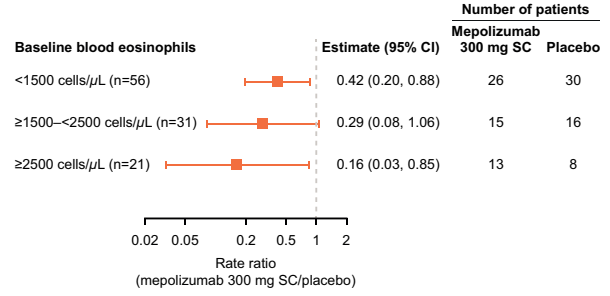
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8 IL, interleukin; OCS, oral corticosteroid.

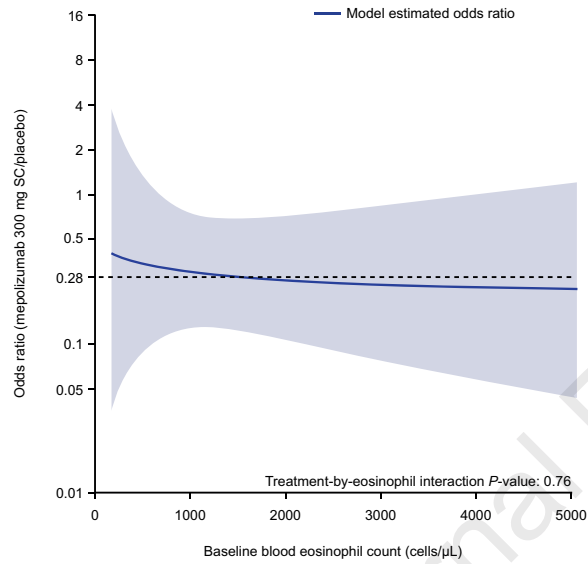
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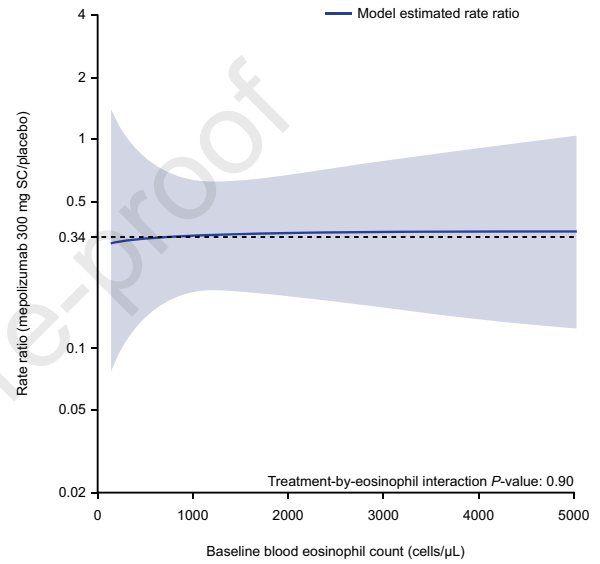
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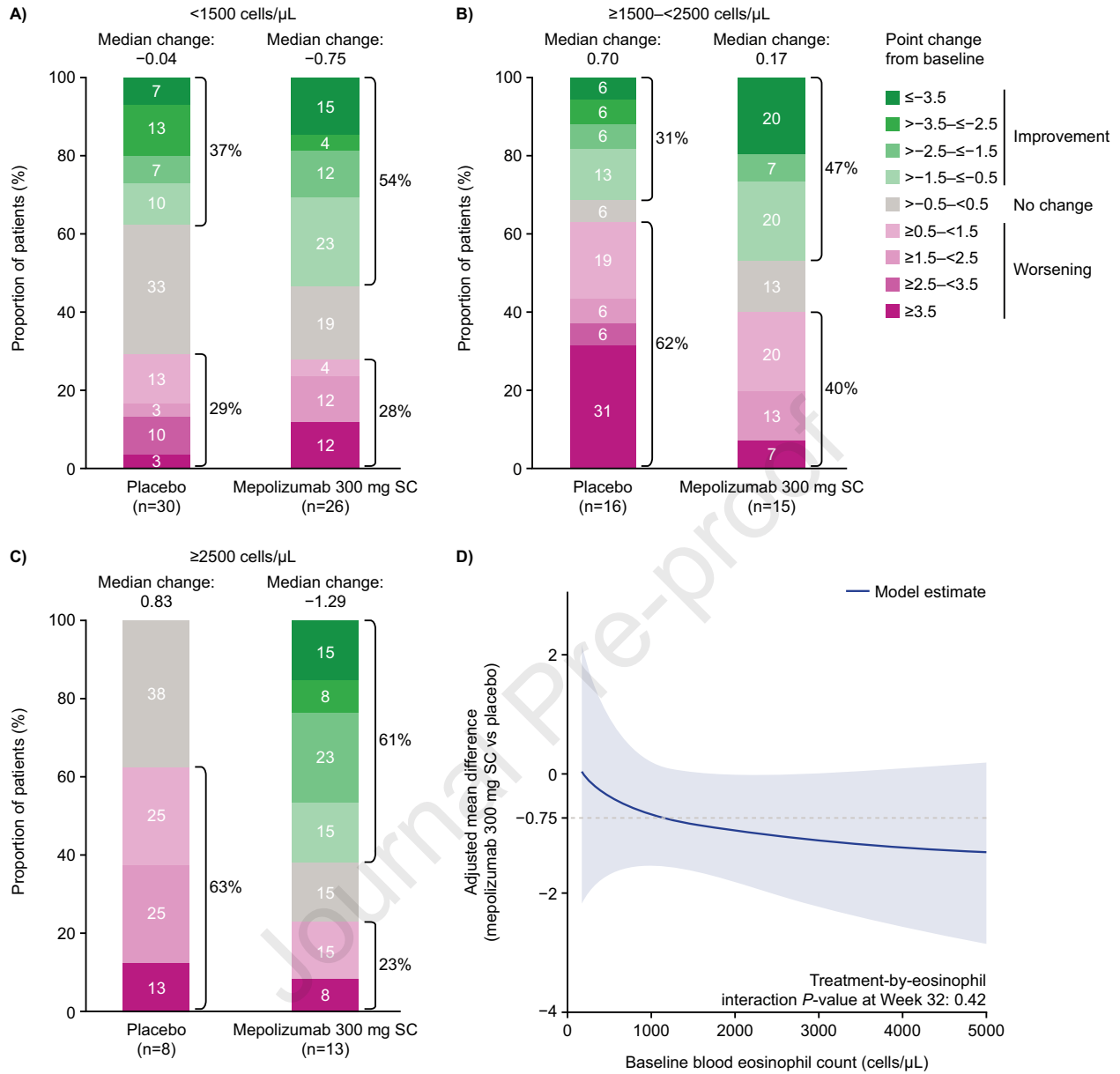


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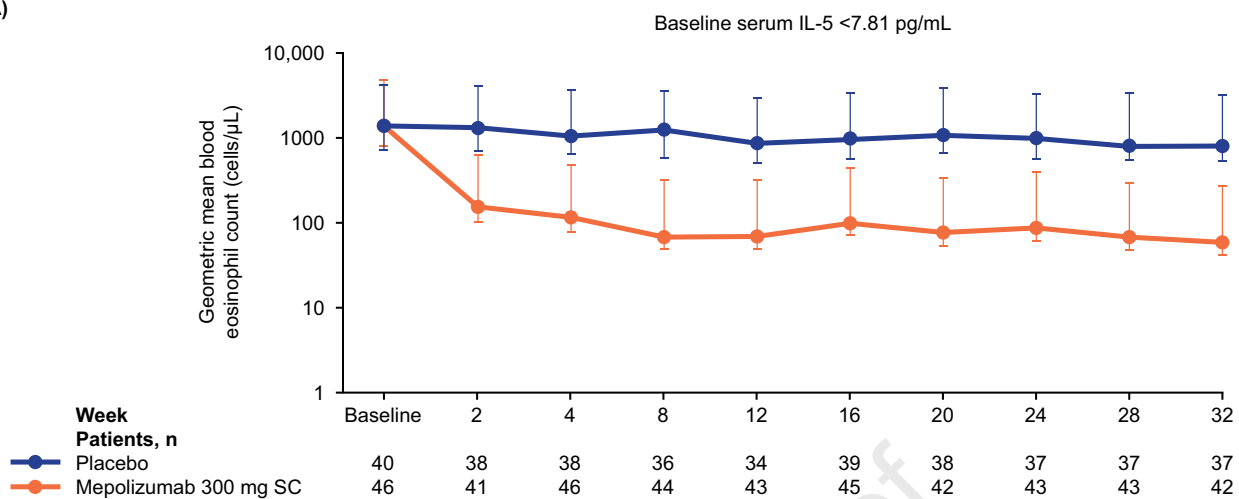


D)





A)



B)

