

Clinical Communications

Clinical effects of mepolizumab in patients with severe eosinophilic asthma according to background therapy: A meta-analysis

Njira Lugogo, MD^{a,*}, Mark C. Liu, MD^b,
Ian Pavord, FMedSci^c, Patrick D. Mitchell, MD^d,
Steven G. Smith, PhD^e, Stephen Mallett, MSc^f,
Frank C. Albers, MD, PhD^g,
Eric S. Bradford, MD, MSc, MBA^{e,*},
Steven W. Yancey, MSc^e, and Elisabeth H. Bel, MD, PhD^h

Clinical Implications

Mepolizumab improves clinical outcomes in patients with severe eosinophilic asthma regardless of their background therapies (number and type of background controller therapies). Among patients with a high blood eosinophil count, mepolizumab reduced exacerbations with use and nonuse of maintenance oral corticosteroids.

Mepolizumab is an IL-5 antagonist mAb indicated for add-on maintenance treatment for patients with severe eosinophilic asthma and refractory eosinophilic granulomatosis with polyangiitis.¹ The Steroid Reduction with Mepolizumab Study (SIRIUS) trial (NCT01691508) demonstrated that mepolizumab reduced the maintenance oral corticosteroid (OCS) dose required for OCS-dependent patients with severe eosinophilic asthma, as well as the exacerbation rate.² Other phase 2 and 3 trials including Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) (NCT01691521), Mepolizumab Adjunctive Therapy in Subjects with Severe Eosinophilic Asthma on Markers of Asthma Control (MUSCA) (NCT02281318), and Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma (DREAM) (NCT01000506) showed that mepolizumab plus standard of care therapy reduced exacerbations in patients with severe eosinophilic asthma.³⁻⁵ With clinical experience, there has been increasing interest in understanding the different baseline disease characteristics that are associated with efficacy outcomes. A previously published meta-analysis of the MENSA and MUSCA trials (208115) suggested that mepolizumab treatment effects versus placebo were generally greater in patients with higher baseline blood eosinophil counts (BECs), which may indicate higher disease morbidity, compared with those with lower counts.⁶ To investigate the effect of the type and number of background therapies, as well as maintenance OCS use on the efficacy of mepolizumab, we performed a post hoc analysis using data from this published meta-analysis.⁶ An additional meta-analysis of the DREAM, MENSA, and MUSCA trials (213079) was also performed to assess the impact of maintenance OCS use and dose and BEC on the efficacy of mepolizumab.

DREAM (phase 2b/3), MENSA, and MUSCA (phase 3) were randomized, double-blind, placebo-controlled trials enrolling

patients aged 12 years or greater with severe eosinophilic asthma. Patients had two or more exacerbations requiring systemic corticosteroids despite treatment with inhaled corticosteroids and one or more controller therapy in the previous year, a BEC of 150 cells/ μ L or more at screening (MENSA and MUSCA only) or 300 cells/ μ L or more in the prior year, and evidence of airflow obstruction. DREAM included additional criteria for defining eosinophilic inflammation (see [Supplementary Information](#) trial exclusion criteria in this article's Online Repository at www.jaci-inpractice.org).⁵ Patients received mepolizumab or matched placebo, plus standard care, every 4 weeks: in DREAM, mepolizumab 75, 250, or 750 mg intravenously for 52 weeks; in MENSA, mepolizumab 75 mg intravenously or 100 mg subcutaneously for 32 weeks; and in MUSCA, mepolizumab 100 mg subcutaneously for 24 weeks. Only the mepolizumab 100 mg subcutaneous dose was included in the meta-analysis of the MENSA and MUSCA trials, because at the time of analysis, this was the approved dose for severe eosinophilic asthma, whereas the meta-analysis of DREAM, MENSA, and MUSCA included the 75-mg intravenous dose from DREAM and MENSA. The mepolizumab 75-mg intravenous dose group was included to provide precision in the analysis and was justified on the basis of bioequivalence of the 100-mg subcutaneous and 75-mg intravenous doses.⁷ The primary endpoint in DREAM and MENSA was the clinically significant exacerbation rate (defined as starting systemic corticosteroids for 3 or more days [or a twofold or greater increase in dose for patients already receiving maintenance OCS], and/or an emergency room visit or hospitalization), and in MUSCA, it was St George's Respiratory Questionnaire. Blood eosinophil count was an additional endpoint. Exacerbation and BEC endpoints were assessed as part of this analysis.

Clinically significant exacerbations were evaluated according to the number and types of background controller therapies used (including tablets and injectables) in the post hoc meta-analysis of MENSA and MUSCA (208115). Separately, exacerbations were also analyzed by baseline maintenance OCS (using or not using) and by baseline maintenance OCS dose categories ($>0\text{--}\leq 7.5$, $>7.5\text{--}\leq 15$, and >15 mg/d) and baseline BEC (<300 and ≥ 300 cells/ μ L) ([Supplementary Information](#)) in the post hoc meta-analysis of DREAM, MENSA, and MUSCA (213079). In addition, in the DREAM, MENSA, and MUSCA meta-analysis, the exacerbation rate was modeled using BEC on a continuous scale with baseline maintenance OCS (using or not using) terms in the model. Statistical analyses are described in the [Supplementary Information](#).

Patients receiving a higher number of background therapies at baseline had a higher burden of disease compared with those receiving a lower number, as indicated by the respective exacerbation rates in the year before study entry and the proportions of patients receiving maintenance OCS at baseline (see [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org). Patients receiving maintenance OCS at baseline had a higher burden of disease compared with those not receiving maintenance OCS, with higher exacerbation rates in the previous year and worse Asthma Control Questionnaire-5 scores and St George's Respiratory Questionnaire total scores.

Mepolizumab reduced clinically significant exacerbations compared with placebo regardless of the type and number of background therapies ([Figure 1, A](#)), or maintenance OCS use or non-use ([Figure 1, B](#)). Within the greater than 0 to 7.5 or less mg/

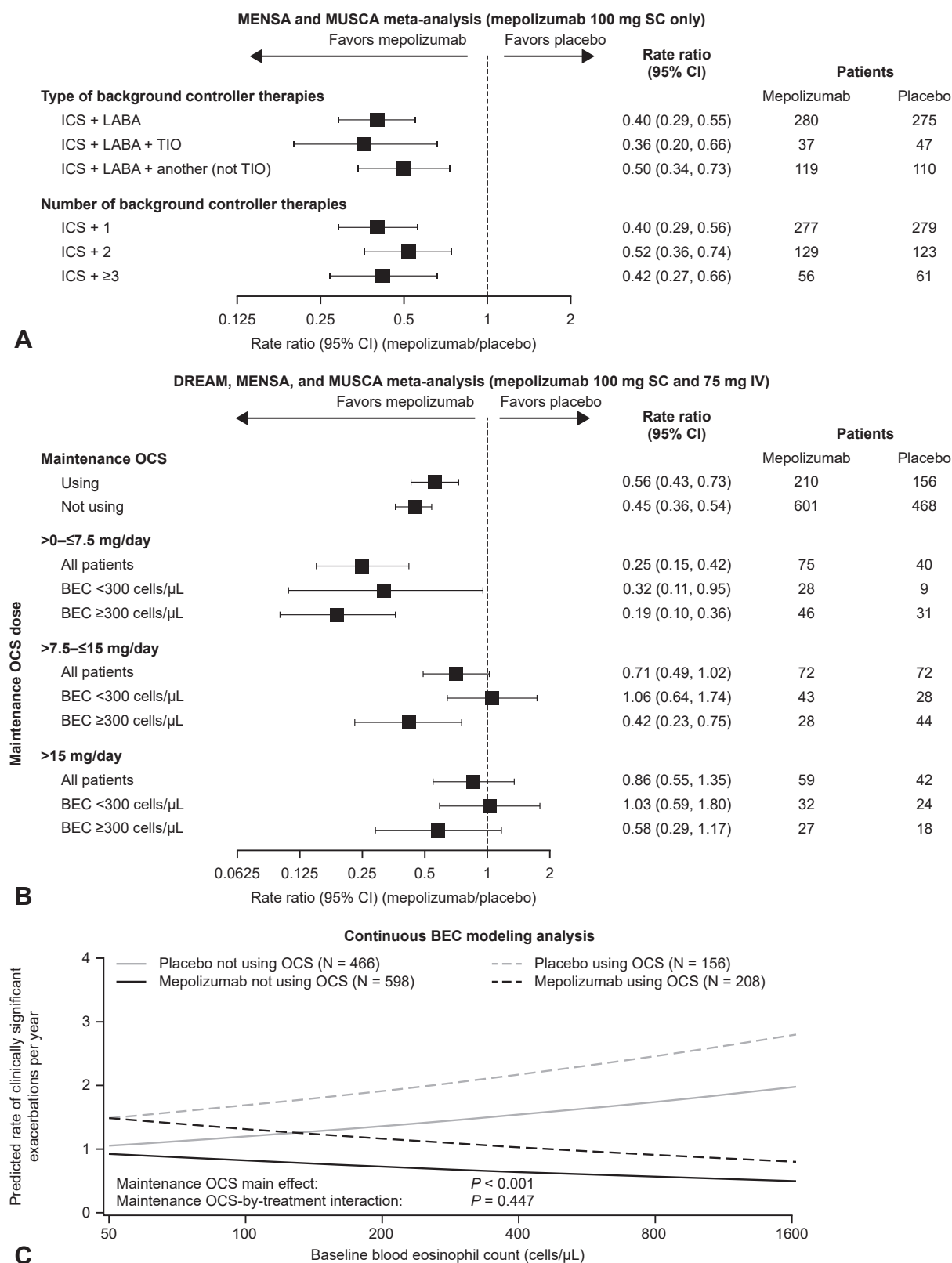


FIGURE 1. Rate of clinically significant exacerbations according to type and number of background controller therapies (**A**); and use of maintenance oral corticosteroid (OCS) (using or not using), and maintenance OCS dose category and blood eosinophil count (BEC) at baseline (**B**); and predicted rate of clinically significant exacerbations per year against baseline BEC (**C**). Patient numbers are on the right in (A) and (B). 95% confidence intervals (CIs) are in parentheses in (B). Data in (C) are from the intent-to-treat populations from the Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma (DREAM), Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA), and Mepolizumab Adjunctive Therapy in Subjects with Severe Eosinophilic Asthma on Markers of Asthma Control (MUSCA) studies. Seven patients with missing baseline BECs were excluded from this analysis. *ICS*, inhaled corticosteroid; *IV*, intravenous; *LABA*, long-acting β -agonist; *SC*, subcutaneous; *TIO*, tiotropium.

TABLE I. BEC after treatment according to baseline BEC and maintenance OCS dose categories at baseline*

Subgroups	Geometric mean BEC (cells/ μ L)					
	Maintenance OCS ($>0\text{--}\leq 7.5$ mg/d)		Maintenance OCS ($>7.5\text{--}\leq 15$ mg/d)		Maintenance OCS (>15 mg/d)	
	Placebo	Mepolizumab	Placebo	Mepolizumab	Placebo	Mepolizumab
All patients						
Baseline	470 (n = 40)	360 (n = 74)	310 (n = 72)	180 (n = 71)	220 (n = 42)	210 (n = 59)
End of study	280 (n = 37)	50 (n = 71)	240 (n = 67)	40 (n = 65)	170 (n = 32)	50 (n = 48)
Baseline BEC <300 cells/ μ L						
Baseline	200 (n = 9)	150 (n = 28)	100 (n = 28)	90 (n = 43)	120 (n = 24)	100 (n = 32)
End of study	220 (n = 7)	40 (n = 27)	170 (n = 26)	30 (n = 39)	130 (n = 20)	40 (n = 23)
Baseline BEC ≥ 300 cells/ μ L						
Baseline	600 (n = 31)	630 (n = 46)	640 (n = 44)	540 (n = 28)	540 (n = 18)	500 (n = 27)
End of study	300 (n = 30)	50 (n = 44)	300 (n = 41)	60 (n = 26)	300 (n = 12)	60 (n = 25)

BEC, blood eosinophil count; OCS, oral corticosteroid.

*Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma, Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma, and Mepolizumab Adjunctive Therapy in Subjects with Severe Eosinophilic Asthma on Markers of Asthma Control (mepolizumab 100 mg subcutaneously and 75 mg intravenously). Data for 2 patients receiving placebo and 4 receiving mepolizumab were missing owing to unknown baseline OCS dose. One additional mepolizumab patient was omitted owing to an unknown baseline BEC.

d maintenance OCS dose category, reductions were seen in the all-patient group and in the two BEC threshold groups, whereas in higher OCS dose categories, effects differed between BEC threshold groups. In the greater than 7.5 to 15 or less mg/d category, a clinically relevant reduction of 58% was seen in the 300 or greater cells/ μ L BEC group but not in the less than 300 cells/ μ L BEC group. A clinically relevant reduction was also observed in the greater than 15 mg/d category, with a 42% numerical reduction in the 300 or greater cells/ μ L BEC group (Figure 1, B). The continuous BEC modeling analysis demonstrated greater reductions in the predicted rates of exacerbations with mepolizumab compared with placebo with increasing baseline BEC, with no additional effect of baseline OCS use on the treatment effect ($P = .447$) (Figure 1, C). In addition, modeling the exacerbation rate using BEC on a continuous scale with baseline maintenance OCS dose categories ($>0\text{--}\leq 7.5$, $>7.5\text{--}\leq 15$, and >15 mg/d) demonstrated greater reductions in the predicated exacerbation rate with mepolizumab versus placebo with increasing BEC, regardless of the OCS dose category (data not shown). Mepolizumab reduced BEC to similar levels (30–60 cells/ μ L) across all maintenance OCS dose categories, regardless of baseline BEC (Table I).

Overall, data from these two meta-analyses demonstrate that mepolizumab reduced the exacerbation frequency and BEC compared with placebo in patients with severe eosinophilic asthma regardless of the disease burden before the initiation of mepolizumab treatment, as indicated by the number and type of background therapies, and maintenance OCS use or nonuse. Patients in the highest maintenance OCS dose category had lower baseline BEC compared with the lowest maintenance OCS dose category, and potentially more refractory disease than those receiving lower doses, which may explain the limited mepolizumab treatment effect in this category, because mepolizumab efficacy is known to depend on baseline BEC.⁶ The modeling analysis confirmed that baseline maintenance OCS use is a prognostic factor in terms of the overall exacerbation rate ($P < .001$) (Figure 1, C). However, in high-OCS dose patients with high BEC, there was a clinically relevant, although not statistically significant 42% numerical reduction in exacerbations, highlighting that the effect of OCS dose was confounded by BEC, as previously demonstrated.⁸

Because severe asthma is a heterogeneous and chronic disease, individualized and optimized therapy is required to keep asthma symptoms well controlled. However, if symptoms remain uncontrolled even after this treatment,⁹ patients may initiate mepolizumab treatment alongside other asthma medications, and patients could have differing levels of disease burden.⁹ Results from these meta-analyses provide further evidence for the efficacy of mepolizumab in patients with severe eosinophilic asthma receiving different background therapies. Because data are post hoc from meta-analyses of subgroups, caution should be used when interpreting the results clinically. In addition, two different doses of mepolizumab (via two different administration methods) were included. This meta-analysis indicates that mepolizumab has substantial clinical benefits in patients with severe eosinophilic asthma, irrespective of the type or number of background therapies. Exacerbation reductions with mepolizumab compared with placebo increased with increasing baseline BEC counts, irrespective of OCS use.

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^aDepartment of Medicine, Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, Mich

^bDivisions of Allergy and Clinical Immunology, Pulmonary and Critical Care Medicine, Johns Hopkins Asthma and Allergy Center, Baltimore, Md

^cRespiratory Medicine Unit and Oxford Respiratory NIHR BRC, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

^dCumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

^eRespiratory Therapeutic Area, GSK, Research Triangle Park, NC

^fResearch and Development, Statistics, Programming, and Data Standards, GSK, Stockley Park West, Uxbridge, Middlesex, United Kingdom

^gMedical Department, Avillion US Inc, Northbrook, Ill

^hDepartment of Respiratory Medicine, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands

^{*}Currently affiliated with Aeglea BioTherapeutics, Austin, Tex.

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Corresponding author: Njira Lugogo, MD, Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Michigan, 300 North Ingalls St, Ste 2c40, Ann Arbor, Mich 48109. E-mail: nlugogo@med.umich.edu.

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SUPPLEMENTARY INFORMATION**Additional criteria for defining eosinophilic inflammation in the Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma trial**

In addition to a blood eosinophil count (BEC) of 300 cells/ μ L or greater in the prior year, eosinophilic inflammation was defined by any of the following criteria at Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma (DREAM) study entry or in the previous year: a sputum eosinophil count of 3% or more, an exhaled nitric oxide concentration of 50 parts per billion or more, or prompt deterioration of asthma control after a 25% reduction or less in regular maintenance inhaled or oral corticosteroids (OCS).

Trial exclusion criteria

Patients were excluded from the DREAM, Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA), and Mepolizumab Adjunctive Therapy in Subjects with Severe Eosinophilic Asthma on Markers of Asthma Control (MUSCA) trials if they were current or former smokers with a smoking history of 10 or more pack-years; had known preexisting, clinically important lung conditions other than asthma; had a current malignancy or a history of cancer; had clinically significant cardiovascular, endocrine, autoimmune, metabolic, neurologic, renal, gastrointestinal, hepatic, hematologic, or any other system abnormalities that were uncontrolled with standard treatment; had other conditions that could lead to elevated eosinophils, such as hypereosinophilic syndromes, including eosinophilic granulomatosis with polyangiitis, or eosinophilic esophagitis (the DREAM trial excluded patients with a diagnosis of eosinophilic granulomatosis with polyangiitis only); or had a known, preexisting parasitic infestation within 6 months before visit 1 of the study. Patients were also excluded from the DREAM trial if they had regular use of oral or systemic corticosteroids for diseases other than asthma within the past 12 months or any intra-articular, short-acting intramuscular corticosteroid within 1 month or intramuscular, long-acting depot corticosteroids within 3 months. In addition, patients were excluded if they had received omalizumab or any other biologic for the treatment of inflammatory disease within 130 days of visit 1 of the DREAM

trial or had received omalizumab within 130 days of visit 1 or any mAb (other than omalizumab) to treat inflammatory disease within five half-lives of visit 1 of the MENSA and MUSCA trials. Individuals with a known lack of adherence to controller medications and/or ability to follow physician's recommendations were also excluded. The full list of exclusion criteria can be found in the relevant papers.

Baseline BEC threshold

The baseline BEC threshold of 300 cells/ μ L was selected for analysis in the meta-analysis of the DREAM, MENSA, and MUSCA trials based on the median; this was to give equal numbers (median value) in each subgroup.

Statistical analysis

In the meta-analysis of MENSA and MUSCA, the annual rate of exacerbations was analyzed using a negative binomial regression model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs no OCS), exacerbations in the year before the study (as an ordinal variable), and baseline percent predicted forced expiratory volume in 1 second (FEV₁), with logarithm of time receiving treatment as an offset variable. Rates were compared using an inverse variance weighted fixed-effects meta-analysis. For the meta-analysis of data from DREAM, MENSA, and MUSCA, the covariates were study ID, treatment group, region, exacerbations in the year before the study (as an ordinal variable), and baseline percent predicted FEV₁, with logarithm of time receiving treatment as an offset variable.

Exacerbation rates were also modeled as a function of blood eosinophils as a continuous variable using data from DREAM, MENSA, and MUSCA. A negative binomial generalized linear model was used with covariates of study ID, treatment group, region, exacerbations in the year before the study (as an ordinal variable), baseline percent predicted FEV₁, with logarithm of time receiving treatment as an offset variable. In addition, the log-transformed baseline BEC, baseline maintenance OCS (using or not using), and their interactions with treatment were included in the model. Moreover, this analysis was repeated using OCS dose categories ($>0\text{--}\leq 7.5$, $>7.5\text{--}\leq 15$, and >15 mg/d) in place of OCS (using or not using).

TABLE E1. Demographics and baseline disease characteristics for intent-to-treat (ITT) population from meta-analysis of Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) and Mepolizumab Adjunctive Therapy in Subjects with Severe Eosinophilic Asthma on Markers of Asthma Control (MUSCA) trials (208115) according to background therapies and use of maintenance oral corticosteroids (OCS), and ITT population from meta-analysis of Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma (DREAM), MENSA, and MUSCA trials (213079) according to maintenance OCS use and dose category and baseline blood eosinophil count

Characteristic	MENSA and MUSCA trials ^{E1,E2} (208115) (mepolizumab 100 mg subcutaneously)			DREAM, MENSA, and MUSCA trials ^{E1-E3,*} (213079) (mepolizumab 100 mg subcutaneously and 75 mg intravenously)				
	ICS plus number of background controller therapies [†]			Maintenance OCS		Maintenance OCS dose category at baseline (mg/d) [‡]		
	ICS + 1 (n = 556/936)	ICS + 2 (n = 252/936)	ICS + ≥3 (n = 117/936)	Using (n = 366/1435)	Not using (n = 1069/1435)	>0-≤7.5 (n = 115/360)	>7.5-≤15 (n = 144/360)	>15 (n = 101/360)
Age, y (mean [SD])	50.1 (13.95)	51.4 (13.84)	51.3 (13.51)	51.7 (11.87)	49.5 (13.87)	54.1 (12.12)	51.8 (10.77)	48.9 (12.05)
Female, n (%)	338 (61)	140 (56)	64 (55)	195 (53)	659 (62)	62 (54)	78 (54)	52 (51)
Asthma duration, y (mean [SD])	20.0 (14.77)	19.1 (13.59)	19.9 (14.59)	18.3 (14.33)	19.9 (14.17)	N/A	N/A	N/A
Exacerbations in previous year (mean [SD]) n (%)	2.8 (1.75)	3.5 (2.58)	4.3 (3.10)	4.1 (3.49)	3.1 (2.10)	N/A	N/A	N/A
2	364 (65)	119 (47)	32 (27)	128 (35)	611 (57)	50 (43)	46 (32)	30 (30)
3	103 (19)	52 (21)	34 (29)	90 (25)	231 (22)	29 (25)	35 (24)	26 (26)
≥4	89 (16)	81 (32)	51 (44)	148 (40)	227 (21)	36 (31)	63 (44)	45 (45)
Receiving maintenance OCS therapy at baseline, n (%)	101 (18)	83 (33)	41 (35)	366 (100)	0	115 (100)	144 (100)	101 (100)
Daily dose, mg/d, median	N/A	N/A	N/A	10	N/A	5	10	24
Pre-bronchodilator forced expiratory volume in 1 s, % predicted (mean [SD])	59.6 (15.66)	58.9 (18.01)	59.7 (19.22)	56.0 (17.41)	61.0 (16.34)	58.5 (15.78)	56.4 (17.31)	51.9 (18.54)
St George's Respiratory Questionnaire total score (mean [SD]) [§]	45.0 (17.94)	50.0 (19.49)	50.0 (20.81)	52.2 (17.97)	44.8 (19.04)	N/A	N/A	N/A
Asthma Control Questionnaire-5 score (mean [SD])	2.15 (1.089)	2.35 (1.263)	2.36 (1.295)	2.42 (1.189)	2.18 (1.127)	2.1 (1.09)	2.3 (1.15)	3.0 (1.15)
Blood eosinophil count, cells/μL (geometric mean [SD logs])	330 (0.918)	310 (0.944)	350 (1.002)	290 (1.020)	310 (0.919)	400 (0.856)	250 (1.149)	230 (0.938)

*Only the mepolizumab doses of 75 mg intravenously and 100 mg subcutaneously were included in this analysis.

[†]Baseline data were missing for 11 patients. Two patients had unknown inhaled corticosteroids and/or controller medication status at baseline.

[‡]Two patients receiving placebo and four receiving mepolizumab are omitted from the table because their baseline OCS dose was unknown.

[§]St George's Respiratory Questionnaire data were collected only in the MENSA and MUSCA studies. N/A, not available.

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