

Clinical Commentary Review

Clinical Development of Mepolizumab for the Treatment of Severe Eosinophilic Asthma: On the Path to Personalized Medicine

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The development of mepolizumab, an anti-IL-5 monoclonal antibody for the treatment of severe eosinophilic asthma, is an example of a clinical development program that evolved over time based on sound, basic scientific principles. Initial clinical data on the effects of mepolizumab on lung function in a general asthmatic population were disappointing. However, it became clear that mepolizumab may be more effective against other clinical endpoints, particularly asthma exacerbations, in patients with more severe disease. Furthermore, a developing understanding of asthma disease pathobiology led to the identification of an appropriate target population and predictive biomarker for mepolizumab treatment: patients with severe eosinophilic asthma and blood eosinophil count. Mepolizumab use provides clinically meaningful benefits in this target population, fulfilling an unmet need. This Clinical Commentary Review describes the clinical development of mepolizumab and details of how this program informed the development of other

biologic therapies in patients with severe asthma. This account highlights how a personalized approach toward treatment of patients with severe eosinophilic asthma, supported by a large body of scientific evidence, ultimately led to new and effective treatments and improved patient outcomes. © 2020 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-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Mepolizumab; Anti-IL-5; Biologic therapy; Severe eosinophilic asthma

For patients with severe asthma who experience poor symptom control and/or frequent asthma exacerbations, the addition of biologic therapies to controller medication is becoming the

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Editorial support (in the form of writing assistance, including development of the initial draft from the author discussions, assembling tables and figures, collating authors' comments, grammatical editing, and referencing) was provided by Nathan Ley, PhD, and Elizabeth Hutchinson, PhD, CMPP, at Fishawack Indicia Ltd, UK, and was funded by GlaxoSmithKline.

Conflicts of interest: I. D. Pavord received fees for speaking from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, Teva, Chiesi, Sanofi, Regeneron, and GlaxoSmithKline (GSK); fees for organizing educational events from AstraZeneca and Teva; honoraria for attending advisory panels with Genentech, Regeneron, AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Teva, Merck, Sanofi, Circassia, Chiesi, and Knopp; sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, AstraZeneca, Teva, and Chiesi; and a research grant from Chiesi. A. Menzies-Gow has attended advisory boards for GSK, Novartis, AstraZeneca, Boehringer Ingelheim, Teva, and Sanofi; has received speaker fees from Novartis, AstraZeneca, Vectura, Boehringer Ingelheim, and Teva; has participated in research for which his host institution has been remunerated with Hoffman La Roche, GSK, Boehringer Ingelheim, and AstraZeneca; has attended international conferences sponsored by Teva and Boehringer Ingelheim; and has consultancy agreements with AstraZeneca, Vectura, and Sanofi. R. Buhl received personal fees from AstraZeneca, Chiesi, Cipla, Sanofi, and Teva; grants and personal fees from Boehringer Ingelheim, Novartis,

and Roche; and grants from GSK, all of which are outside the submitted work. P. Chanez provided consultancy services for Boehringer Ingelheim, Johnson & Johnson, GSK, Merck Sharp & Dohme, AstraZeneca, Novartis, Teva, Chiesi, and Sanofi; has served on advisory boards for Almirall, Boehringer Ingelheim, Johnson & Johnson, GSK, AstraZeneca, Novartis, Teva, Chiesi, and Sanofi; has received lecture fees from Boehringer Ingelheim, Centocor, GSK, AstraZeneca, Novartis, Teva, Chiesi, Boston Scientific, and ALK-Abelló; and received industry-sponsored grants from Roche, Boston Scientific, Boehringer Ingelheim, Centocor, GSK, AstraZeneca, ALK-Abelló, Novartis, Teva, and Chiesi. M. Dransfield received grants from the American Lung Association, Department of Defense, Department of Veterans Affairs, and National Institutes of Health; personal fees from AstraZeneca, GlaxoSmithKline, Mereo, PneumRx/BTG, Pulmonx, and Quark; and contracted clinical trial support from AstraZeneca, Boehringer Ingelheim, Gala, GlaxoSmithKline, Mereo, Nuvaira, PneumRx/BTG, Pulmonx, and Yungjin. N. Lugogo received grant support and advisory board fees from GlaxoSmithKline, Genentech, and Sanofi-Regeneron; grant support, consulting fees, and advisory board fees from AstraZeneca; consulting fees and advisory board fees from Teva Pharmaceuticals; and advisory board fees from Novartis. O. N. Keene and S. W. Yancey are current employees of GSK and hold stocks/shares in GSK. E.S. Bradford was an employee of GlaxoSmithKline during the writing of this review paper and is now employed by Aeglea BioTherapeutics.

Received for publication April 15, 2020; revised July 15, 2020; accepted for publication August 12, 2020.

Available online ■■

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Abbreviations used

ACQ- Asthma Control Questionnaire
 AE- Adverse event
 AI- Autoinjector
 CI- Confidence interval
 FeNO- Fractional exhaled nitric oxide
 FEV₁- Forced expiratory volume in 1 second
 ICS- Inhaled corticosteroid
 IV- Intravenous
 OCS- Oral corticosteroid
 PD- Pharmacodynamic
 PK- Pharmacokinetic
 SC- Subcutaneous
 SGRQ- St George's Respiratory Questionnaire

new standard of care.¹ Omalizumab (which neutralizes IgE) was the first biologic available for patients with uncontrolled asthma.^{2,3} Biologic therapies that neutralize IL-5 signaling (mepolizumab and reslizumab) or bind to the IL-5 receptor (benralizumab), thereby reducing eosinophil counts in blood and airways, were then developed and approved for treatment in patients with severe eosinophilic asthma.⁴⁻⁶ More recently, an IL-4 receptor alpha antagonist (dupilumab), which inhibits IL-4 and IL-13 signaling, has been approved for treatment of moderate-to-severe eosinophilic or oral corticosteroid (OCS)-dependent asthma in the USA.⁷

Treatment strategies for patients with asthma continue to shift toward personalized medicine-based approaches; these depend on the identification of modifiable patient characteristics (treatable traits), often using biomarkers.^{8,9} For example, in the Global Initiative for Asthma guidelines, anti-IL-5/IL-5 receptor therapies are recommended for those who have multiple severe exacerbations in the prior year and blood eosinophils above a specific threshold.^{1,10} Omalizumab is targeted to patients who have specific total IgE counts (although this biomarker has not been shown to be associated with treatment efficacy¹¹), and dupilumab is targeted to patients with specific blood eosinophil counts and fractional exhaled nitric oxide (FeNO) levels.¹ In each case, a specific therapy is recommended for a population with a given phenotype (eg, eosinophilic or allergic asthma), although these populations overlap.¹²

Mepolizumab was the first monoclonal antibody developed to target IL-5 and is indicated for the treatment of severe eosinophilic asthma in children and adults 6 years of age and older.^{4,13} The patient population with asthma who benefits from mepolizumab is now defined; however, this population was not clear at the start of the clinical development of mepolizumab and progress required important changes to the way asthma symptoms, exacerbations, and eosinophilic airway inflammation were viewed. This review will: (1) examine how mepolizumab progressed to become established and firmly considered as first-in-class therapy for a specific patient population and (2) describe how a new understanding of the role of eosinophils in asthma pathology led to the successful clinical development of other biologic agents.

EARLY RESEARCH: THE ROLE OF EOSINOPHILS IN AIRWAY INFLAMMATION

The role of eosinophils as an important cellular player in asthma was confirmed in the 1980s, with evidence showing that

activated eosinophils secrete proteins that can damage bronchial epithelium.¹⁴ Subsequently, blood and bronchoalveolar eosinophil counts were shown to be correlated with asthma severity, suggesting that eosinophils are pivotal and critical effector cells in asthma airway inflammation.^{15,16} Separately, *in vitro* experiments demonstrated that cytokines including IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor could stimulate eosinophil production in bone marrow cultures, with only IL-5 implicated as specific for eosinophil differentiation and maturation.¹⁷ Expression of IL-5 mRNA in bronchial biopsy was subsequently shown to correlate with clinical features of asthma, and IL-5 became firmly established as a potential target for the development of antieosinophil therapies.^{17,18}

ESTABLISHING THE EFFICACY OF IL-5 INHIBITION IN ASTHMA

Establishing the patient population and an appropriate trial endpoint

In early 2000, the precise role of reducing eosinophil counts in the treatment of asthma was uncertain. A randomized trial undertaken by Leckie et al,¹⁹ in patients with mild asthma, found that a single injection of mepolizumab intravenously (IV, up to 10 mg/kg) could reduce eosinophil counts in the airway and blood for at least a month; however, it was not efficacious in improving forced expiratory volume in 1 second (FEV₁), the airway bronchoconstrictor response to allergen, or airway responsiveness to histamine compared with placebo. Furthermore, a subsequent multicenter, randomized, double-blind, placebo-controlled study²⁰ in patients with moderate asthma managed with inhaled corticosteroids (ICS), selected on the basis of the presence of bronchodilator responsive airflow limitation, reported that mepolizumab did not improve pulmonary function endpoints or symptoms. In this study, however, the relatively small number of patients experiencing exacerbations between weeks 0 and 20 was numerically lower in the mepolizumab 750 mg IV group (11 patients, 10%) compared with placebo (20 patients, 16%). This observation contributed to a developing concept that anti-IL-5 therapy should be targeted to a more severe population experiencing frequent exacerbations.

In parallel, a new understanding of the relationship between asthma symptoms, exacerbations, and eosinophilic airway inflammation was evolving as a result of the development of a noninvasive method to assess airway inflammation using induced sputum.^{8,21} Cross-sectional studies showed that eosinophilic airway inflammation was present in around 50% of patients with asthma²² and that its presence did not relate closely to symptoms or the presence of variable airflow limitation but did relate to the likelihood of an asthma exacerbation and also to the response to corticosteroids.^{23,24} Moreover, an interventional study in patients with moderate-to-severe asthma comparing symptom- and inflammation-guided corticosteroid treatment showed that the main clinical consequence of reducing eosinophilic airway inflammation was a reduced risk of asthma exacerbations.²⁵ Similarly, several studies have demonstrated that levels of eosinophilic airway inflammation can predict asthma control after ICS discontinuation.^{26,27}

These new insights provided a strong basis for a re-examination of the effect of anti-IL-5 therapy on exacerbations in patients selected on the basis of having the relevant treatable trait (eg, eosinophilic airway inflammation) rather than an

unrelated and arbitrary characteristic (eg, bronchodilator responsive airflow limitation). Haldar et al²⁸ conducted a trial in 61 patients with a history of recurrent severe exacerbations and evidence of eosinophilic inflammation based on sputum eosinophilia. The results of the trial were impressive; patients who received mepolizumab experienced significantly fewer severe exacerbations versus placebo after 50 weeks (2.0 vs 3.4 per patient, respectively, $P = .02$), as well as experiencing improvements in quality of life.²⁸ An additional study by Nair et al,²⁹ in patients with asthma who had sputum eosinophilia despite treatment with prednisone and high-dose ICS, showed that compared with placebo, mepolizumab allowed for a reduction in prednisone dose and asthma exacerbations. These studies highlighted the value of focusing on the right patient population and exacerbations as the primary clinical effect as well as the potential steroid-sparing effect of mepolizumab.

Confirming the target population and route of administration

After the realization that anti-IL-5 therapy should be targeted specifically to patients with severe asthma with eosinophilic inflammation, and that an appropriate primary endpoint for the trials should be exacerbations rather than lung function, a larger study was carried out to establish optimal dosing and patient characteristics associated with response to mepolizumab. DREAM (NCT01000506) was a large Phase 2b/3, placebo-controlled, dose-ranging, randomized trial including patients with severe asthma with recurrent exacerbations and blood and/or sputum evidence of eosinophilic inflammation (or alternatively high FeNO levels or history of asthma control deterioration after ICS/OCS reduction) who were receiving high-dose ICS, with or without maintenance OCS, plus additional controllers. Treatment with mepolizumab 75, 250, or 750 mg IV monthly reduced exacerbation rates by 39% to 52% and was well tolerated at all doses examined.³⁰ A multivariate analysis conducted within the DREAM study identified 2 variables associated with increased efficacy: baseline peripheral blood eosinophil count and exacerbation frequency in the previous year.³⁰ Notably, results from the DREAM study suggested that despite similar reductions in the rate of clinically significant exacerbations, mepolizumab did not reduce sputum eosinophil counts to the same extent across all doses,³⁰ suggesting that sputum eosinophils were not the key pharmacodynamic (PD) biomarker for mepolizumab response. Together, these data established a defined phenotype of severe eosinophilic asthma for patients who would be most likely to benefit from anti-IL-5 therapy and identified blood eosinophil count as a potentially useful biomarker for identifying them.

Because subcutaneous (SC) dosing would be the most convenient dosing strategy for patients, a dedicated dose-ranging study was carried out to determine the pharmacokinetic (PK)/PD relationship between mepolizumab SC and blood eosinophil reduction. Patients with asthma and blood eosinophil counts >300 cells/ μ L were randomized to mepolizumab 12.5, 125, or 250 mg SC or 75 mg IV. The 75 mg IV dose gave comparable exposure to 100 mg SC dose based on bioavailability. The route of administration did not affect the dose-response relationship observed.³¹ The PK/PD modeling estimated that 100 mg SC was the dose needed to achieve 90% of the maximal inhibition of blood eosinophils, and therefore this dose was used in further phase 3 studies.³¹

Confirming efficacy of SC dosing in severe eosinophilic asthma

Clinical benefit with anti-IL-5 therapy was further confirmed in 2 subsequent phase 3, randomized, placebo-controlled trials of mepolizumab (Table I). In MENSA (NCT01691521), patients with recurrent asthma exacerbations (≥ 2 in the previous year) and evidence of eosinophilic inflammation (blood eosinophil count ≥ 150 cells/ μ L at screening or ≥ 300 cells/ μ L during the previous 12 months) despite high ICS doses and 3 months of treatment with at least 1 additional controller were included. Patients received mepolizumab 75 mg IV or mepolizumab 100 mg SC or placebo every 4 weeks for 32 weeks.³⁴ Reductions in the annualized rate of exacerbations were similar for both mepolizumab formulations, with reductions of 47% (95% confidence interval [CI]: 28, 60) and 53% (95% CI: 36, 65) with mepolizumab IV and SC, respectively, versus placebo ($P < .001$; primary endpoint). Improvements in quality of life (as measured by the St George's Respiratory Questionnaire [SGRQ] total score; $P < .001$), asthma control (as measured by the Asthma Control Questionnaire [ACQ]-5; $P < .001$), and lung function ($P < .05$) were also seen (Table I).

Following the initial positive results from the Nair et al study,²⁹ the effect of mepolizumab on OCS use was assessed in the phase 3 SIRIUS (NCT01691508) trial. It was important to test this given that OCS represents a burdensome additional therapy associated with negative side effects,³⁵ with a substantial proportion of patients with severe eosinophilic asthma requiring chronic OCS use. In SIRIUS, which included patients with severe eosinophilic asthma who required daily OCS to maintain asthma control, mepolizumab 100 mg SC had a significant OCS-sparing effect and despite this also reduced exacerbations and improved control of asthma symptoms compared with placebo over 20 weeks.³⁶ A reduction in OCS dose was 2.39 times more likely with mepolizumab than with placebo ($P = .008$).

Establishing efficacy beyond exacerbations

Severe asthma has a substantial impact on quality of life, and ensuring that therapies improve quality of life and asthma control, as well as exacerbations, is important to patients.³⁷ Therefore, once the efficacy of anti-IL-5 therapy on improving exacerbations had been established, researchers further assessed how it can improve quality of life. The first study specifically designed to assess the effect of anti-IL-5 therapy on quality of life and asthma control was the mepolizumab MUSCA study.³⁸ This study used the SGRQ to assess quality of life (which has been validated in the severe asthma population)^{39,40} and the ACQ-5 to assess asthma control and found that mepolizumab significantly improved both SGRQ total score and ACQ-5 score (Table I).

Lung function is also an important outcome for asthma studies and was assessed in the MUSCA study.³⁸ During MUSCA, lung function changes were assessed using standardized spirometry equipment across study sites and spirogram over-read, with detailed training of study staff, ensuring that shortfalls in spirometry quality were detected and eliminated. MUSCA showed significant and clinically meaningful benefits of mepolizumab on lung function outcomes (Table I), likely owing to the study being conducted in patients with severe eosinophilic asthma, in contrast to earlier mepolizumab studies that were conducted in broader asthma populations. Since then, further *post hoc* analyses of MENSA and MUSCA have also shown that

TABLE I. Efficacy endpoints across trials for mepolizumab (75 mg, 250 mg, and 750 mg IV; 100 mg SC)

Endpoint	DREAM				MENSA			SIRIUS		MUSCA	
	Placebo	Mepolizumab 75 mg IV	Mepolizumab 250 mg IV	Mepolizumab 750 mg IV	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC	Placebo	Mepolizumab 100 mg SC	Placebo	Mepolizumab 100 mg SC
Baseline disease characteristics											
Exacerbations in previous year, mean (SD)	3.7 (3.8)	3.7 (3.1)	3.4 (2.4)	3.5 (2.8)	3.6 (2.8)	3.5 (2.2)	3.8 (2.7)	2.9 (2.8)	3.3 (3.4)	2.7 (1.5)	2.9 (1.9)
Pre-bronchodilator FEV ₁ % predicted, mean (SD)	59 (15)	60 (16)	59 (17)	61 (16)	62.4 (18.1)	61.4 (18.3)	59.3 (17.5)	57.8 (18.5)	59.6 (17.0)	55.2 (14.6)	55.5 (14.4)
SGRQ total score, mean (SD)	—	—	—	—	46.9 (19.8)	44.4 (19.4)	47.9 (19.4)	45 (18)	50 (18)	46.3 (18.9)	47.4 (18.1)
ACQ-5 score, mean (SD)	2.5 (1.1)	2.2 (1.1)	2.4 (1.1)	2.3 (1.2)	2.28 (1.19)	2.12 (1.13)	2.26 (1.27)	2.0 (1.2)	2.2 (1.3)	2.2 (1.2)	2.2 (1.1)
Blood eosinophil count (cells/ μ L), geo mean (SD log)	280 (1.01)	250 (0.95)	230 (1.20)	250 (0.93)	320 (0.938)	280 (0.987)	290 (1.050)	230 (1.001)	250 (1.245)	350	300
Efficacy endpoints											
Annualized rate of exacerbations, mean (SD)	2.40 (0.11) [‡]	1.24 (0.12) [‡]	1.46 (0.11) [‡]	1.15 (0.12) [‡]	1.74	0.93	0.83	2.12	1.44	1.21	0.51
% reduction, mepolizumab vs placebo, mean (95% CI)	—	52 (39, 69)	61 (46, 81)	48 (36, 64)	—	47 (28, 60)	53 (36, 65)	—	32 (1, 53)	—	58 (44, 69)
Pre-bronchodilator FEV ₁ , change from baseline (mL), mean (SE)	60 (38)	121 (38)	140 (37)	115 (37)	86 (31)	186 (32)	183 (31)	−4 (57)	111 (55)	56 (26)	176 (26)
Difference from placebo (mL), mean (95% CI)	—	61 (−39, 161)	81 (−19, 180)	56 (−43, 155)	—	100 (13, 187)	98 (11, 184)	—	114 (−42, 271)	—	120 (47, 192)
SGRQ total score, change from baseline,* mean (SE)	—	—	—	—	−9.0 (1.2)	−15.4 (1.2)	−16.0 (1.1)	−3.1 (1.7)	−8.8 (1.7)	−7.9 (1.0)	−15.6 (1.0)
Difference from placebo, mean (95% CI)	—	—	—	—	—	−6.4 (−9.7, −3.2)	−7.0 (−10.2, −3.8)	—	−5.8 (−10.6, −1.0)	—	−7.7 (−10.5, −4.9)

ACQ-5, change from baseline, [†] mean (SE)	–0.59 (0.09)	–0.75 (0.09)	–0.87 (0.09)	–0.80 (0.09)	–0.50 (0.07)	–0.92 (0.07)	–0.94 (0.07)	–	–0.40 (0.06)	–0.80 (0.06)
Difference from placebo, mean (95% CI)	–	–0.16 (–0.39, 0.07)	–0.27 (–0.51, 0.04)	–0.20 (–0.43, 0.03)	–	–0.42 (–0.61, –0.23)	–0.44 (–0.63, –0.25)	–	–0.52 (–0.87, –0.17)	–0.4 (–0.6, –0.2)

ACQ, Asthma Control Questionnaire; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; IV, intravenous; MCID, minimal clinically important difference; SC, subcutaneous; SD, standard deviation; SE, standard error; SGRQ, St George's Respiratory Questionnaire.

*MCID = 4 points.³²

†MCID = 0.5 points.³³

‡Mean (SE logs).

mepolizumab improves morning peak expiratory flow when measured 1 week after the first dose.⁴¹

Establishing anti-IL-5 efficacy beyond mepolizumab

The mepolizumab clinical trials have been highly influential in establishing the optimum patient population and outcome measures for trials of the related biologic agents reslizumab and benralizumab. Clinical studies with IV reslizumab and with SC benralizumab in patient populations generally similar to those included in the mepolizumab program have shown benefits in exacerbations and lung function^{42–45} in line with those seen with mepolizumab and, in the case of benralizumab, a similar OCS-sparing effect.⁴⁶ Furthermore, these studies provided evidence of greater efficacy against exacerbations in patients with increasing blood eosinophil counts and more frequent exacerbations, corroborating the use of blood eosinophil counts as a predictive biomarker for response to anti-IL-5/IL-5 receptor therapies.^{42–45,47–49} Quality of life and asthma control were also assessed for benralizumab and reslizumab in their phase III studies and showed improvements in these endpoints; however, unlike MUSCA, the studies were not specifically designed to assess these endpoints and quality of life was assessed using the Asthma Quality of Life Questionnaire rather than the SGRQ.^{43–45,50} The consistency of the clinical outcomes seen with these related biologic agents and their common relationship with predictive biomarkers has firmly established the anti-IL-5/IL-5 receptor approach as a targeted, precision medicine treatment option in patients with severe eosinophilic asthma.

Confirming the relationship between blood eosinophils and clinical efficacy

A close relationship between baseline blood eosinophil count and clinical efficacy has been established with anti-IL-5/IL-5 receptor therapies,^{30,48,51,52} allowing blood eosinophil counts to be used as a predictive biomarker for response.⁹ Although blood eosinophil counts inherently vary over time,⁵³ analyses have demonstrated that a single blood eosinophil count measurement of ≥ 150 cells/ μ L, taken during a period of disease stability, is sufficient in 85% of patients to accurately predict an average count of ≥ 150 cells/ μ L in the following 8 to 12 months, with an average of multiple measurements marginally increasing sensitivity.^{54,55} The utility of blood eosinophil counts as a predictive biomarker for response was initially observed during modeling of exacerbation data in the DREAM study and has been corroborated in additional modeling analyses of the MENSA trial.^{30,34,52} This modeling allows prediction of the size of reduction in exacerbations for specific eosinophil counts; in the DREAM and MENSA studies, respectively, there was an estimated 30% and 39% reduction in clinically significant exacerbations for blood eosinophil counts at 150 cells/ μ L with mepolizumab versus placebo (Figure 1).⁵² The reduction in exacerbations achieved with mepolizumab versus placebo increased progressively from 52% in the group of patients with a baseline blood eosinophil count of ≥ 150 cells/ μ L to 70% in patients with a baseline count of >500 cells/ μ L.⁵² An additional *post hoc* meta-analysis of MENSA and MUSCA has also confirmed the relationship between blood eosinophils specifically for the 100 mg SC dose (Figure 2).⁵⁶ Analyses have also shown that blood eosinophil counts are predictive of improvements in ACQ-5, pre-bronchodilator FEV₁, and peak flow, with the effect of mepolizumab enhanced in those with higher baseline blood eosinophil count.^{38,41,52} Clinical evaluations of reslizumab⁵⁰ and

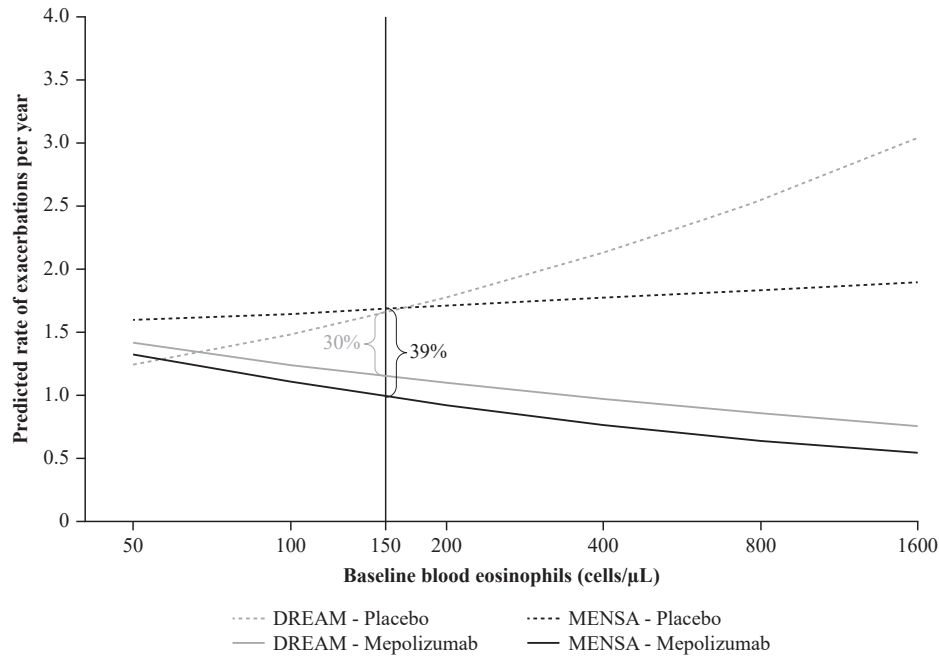


FIGURE 1. Modeling analysis: predicted rate of exacerbations per year against baseline blood eosinophil count in the DREAM and MENSA studies separately. Reprinted from Ortega et al,⁴¹ with permission from Elsevier.

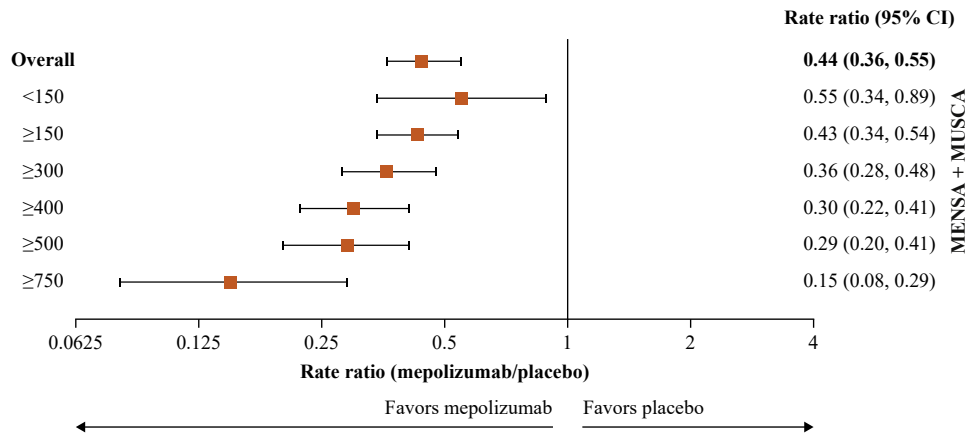


FIGURE 2. Rate ratio (mepolizumab/placebo) of clinically significant exacerbations by baseline blood eosinophil thresholds (meta-analysis of MENSA and MUSCA). Reprinted from Albers et al,⁵⁶ with permission from Elsevier. *CI*, Confidence interval.

benralizumab⁴⁴ targeted a blood eosinophil count of ≥ 400 or ≥ 300 cells/μL, respectively, as thresholds in phase 3 trials for establishing clinical benefit.^{44,50} However, further *post hoc* analysis has shown that the efficacy of benralizumab also increases with increasing blood eosinophil count ≥ 150 cells/μL.⁵¹ Importantly, further clarity on the optimal degree of eosinophil depletion with respect to efficacy and safety is needed,⁹ as is further investigation of the appropriate timing for blood eosinophil count measurement. Nonetheless, the correlation between blood eosinophil count and clinical response to anti-IL-5 therapies is now well established.

Evidence from a *post hoc* analysis of the benralizumab SIROCCO and CALIMA trials also supports the use of exacerbation history as a predictor of treatment response, with the greatest clinical benefit seen in patients with a combination of greater baseline blood eosinophil counts and a history of more frequent exacerbations (similar to that seen in the mepolizumab DREAM trial).⁴⁸ As investigations into the benefits of anti-IL-5 therapies continue, further information on additional clinical characteristics and biomarkers that may predict response to treatment will improve the use of these agents as targeted treatments for patients with severe asthma.

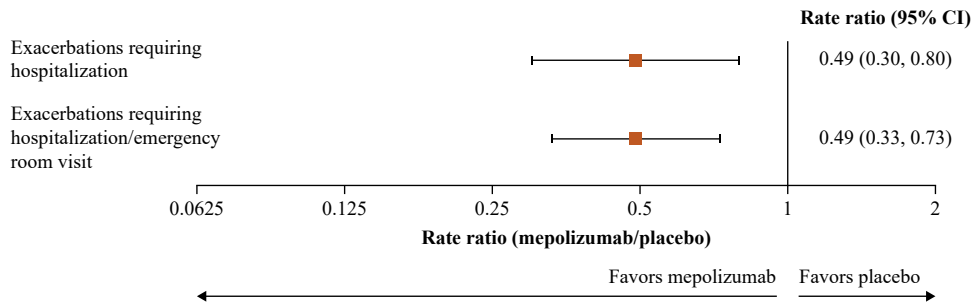


FIGURE 3. Rate ratio (mepolizumab/placebo) of exacerbations requiring hospitalizations and/or emergency room visits (meta-analysis of DREAM, MENSA, SIRIUS, and Haldar et al).⁵⁷ Exacerbations requiring hospitalization include data from DREAM, MENSA, and Haldar et al, 2009; exacerbations requiring hospitalization/emergency room visit include data from DREAM, MENSA, and SIRIUS. *CI*, Confidence interval.

ANTI-IL-5 EFFICACY IN MORE SPECIFIC POPULATIONS

Assessment of anti-IL-5 therapy on more serious exacerbations

Important events such as hospitalizations and emergency room visits are rare and difficult to characterize in single studies. This has been assessed for mepolizumab as there are now a number of studies that allow analysis of these rare events. In a meta-analysis of DREAM, MENSA, SIRIUS, and the study conducted by Haldar et al,²⁸ mepolizumab approximately halved the rate of exacerbations requiring hospitalization (Figure 3).⁵⁷ These reductions are in line with the reductions shown in clinically significant exacerbations in the individual studies, confirming that mepolizumab is efficacious for more severe outcomes in patients with severe eosinophilic asthma.

Assessment of anti-IL-5 therapy according to specific patient characteristics

As the use of anti-IL-5 therapies has increased over time, there has been interest in understanding if their efficacy is affected by different baseline disease characteristics to inform their use in clinical practice. Several *post hoc* meta-analyses of the phase 3 mepolizumab trials have indicated that its efficacy is similar across a range of baseline characteristics defined by body weight/body mass index, baseline OCS use, background controller therapy (eg, ICS, long-acting beta 2 agonist, long-acting muscarinic antagonist, or other), lung function at baseline, presence of comorbid upper airway disease, or a range of other comorbidities including psychopathologies, cardiovascular comorbidities, diabetes, and obesity.⁵⁸⁻⁶¹ Similarly, *post hoc* analyses of the phase 3 benralizumab trials suggest that there is consistent efficacy in patients with and without fixed airflow obstruction⁶² and regardless of IgE concentrations or atopy status.^{63,64} Furthermore, *post hoc* analysis of reslizumab trials suggests greater efficacy in patients with late- versus early-onset asthma,⁶⁵ as well as efficacy in patients with OCS dependence⁴⁹ and in those with refractory eosinophilic asthma.⁶⁶ As such, these 3 anti-IL-5 biologics have demonstrated broad efficacy within the established target population.

Switching from an anti-IgE to an anti-IL-5 targeting biologic

As more biologic therapies were approved for patients with severe asthma, the effect of switching from one therapy to

another was evaluated; this was particularly important as the target population for each therapy can overlap.¹² The open-label, uncontrolled OSMO study (n = 145) confirmed that eligible patients with severe asthma who were not optimally controlled on omalizumab could be effectively switched to mepolizumab to improve their asthma control and quality of life; there was a clinically significant 64% reduction in exacerbations, and 77% and 79% of patients, respectively, achieved the minimum clinically important differences in ACQ-5 (≥ 0.5 points³³) and SGRQ (≥ 4 points³²) scores at week 32.⁶⁷ In addition, a retrospective observational study involving patients with severe asthma who had not responded to omalizumab treatment demonstrated clinically important improvements in exacerbation rates, hospitalizations, FEV₁, and ACQ-5 score when patients were switched from omalizumab to mepolizumab.⁶⁸ Further *post hoc* analyses of the OSMO study have found no evidence that the benefit of switching to mepolizumab depends on prior omalizumab treatment duration⁵⁶ or regimen,⁶⁹ or presence of comorbidities (including aspirin/nonsteroidal anti-inflammatory drugs intolerance, and gastroesophageal reflux disease⁵⁸), with benefits potentially increasing in patients with higher baseline eosinophil counts⁷⁰ or nasal polyps⁵⁸ (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). The effect of switching to reslizumab in patients who failed to respond to omalizumab has also been investigated in an open-label, uncontrolled, pilot study of 29 patients, with 60% of patients achieving asthma control 24 weeks after switching.⁷¹ These effects, seen in patients whose asthma was unresponsive to an IgE-targeting biologic, reflect the direct action of mepolizumab and reslizumab on the IL-5 pathway and highlight the importance and potential of precision medicine in severe asthma.

Long-term efficacy

As anti-IL-5 treatments have become established for the treatment of severe eosinophilic asthma and their use within clinical practice has become more commonplace, attention has turned to the duration of their clinical effects. Long-term efficacy of mepolizumab beyond 1 year of treatment has been assessed in 2 open-label studies: COSMOS (NCT01842607) and the COSMOS extension, COSMEX (NCT02135692), which followed patients for up to 4.8 years after starting treatment with mepolizumab.^{58,72} Both studies showed that long-term treatment with mepolizumab is associated with significant and durable improvements. In COSMEX, the on-treatment

TABLE II. Adverse events and antidrug antibodies with mepolizumab in landmark phase 3 clinical trials

	DREAM				MENSA			SIRIUS		MUSCA	
	Placebo	Mepolizumab 75 mg IV	Mepolizumab 250 mg IV	Mepolizumab 750 mg IV	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC	Placebo	Mepolizumab 100 mg SC	Placebo	Mepolizumab 100 mg SC
All adverse events, n (%)											
On-treatment	121 (78)	126 (82)	126 (83)	122 (78)	158 (83)	161 (84)	152 (78)	61 (92)	57 (83)	207 (74)	192 (70)
Drug related*	26 (17)	28 (18)	29 (19)	33 (21)	30 (16)	33 (17)	39 (20)	12 (18)	21 (30)	25 (9)	31 (11)
Anaphylaxis	0	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0
Serious adverse events, n (%)											
On-treatment	25 (16)	20 (13)	24 (16)	19 (12)	27 (14)	14 (7)	16 (8)	12 (18)	1 (1)	22 (8)	15 (5)
Drug related	0	0	1 (<1)	1 (<1)	1 (1)	0	1 (1)	0	0	1 (<1)	0
Fatal	0	0	2 (1)	1 (<1)	1 (1)	0	0	1 (2)	0	0	0
Most common adverse events,† n (%)											
Nasopharyngitis	24 (15)	34 (22)	33 (22)	29 (19)	46 (24)	45 (24)	33 (17)	10 (15)	10 (14)	46 (17)	31 (11)
Headache	27 (17)	32 (21)	32 (21)	32 (21)	33 (17)	46 (24)	39 (20)	14 (21)	14 (20)	59 (21)	45 (16)
URTI	15 (10)	10 (7)	18 (12)	19 (12)	27 (14)	22 (12)	24 (12)	5 (8)	3 (4)	14 (5)	17 (6)
Sinusitis	16 (10)	10 (7)	10 (7)	12 (8)	18 (9)	11 (6)	18 (9)	6 (9)	7 (10)	12 (4)	11 (4)
Bronchitis	15 (10)	17 (11)	13 (9)	13 (8)	18 (9)	14 (7)	9 (5)	6 (9)	7 (10)	11 (4)	6 (2)
Injection-site reaction	10 (6)	8 (5)	12 (8)	19 (12)	6 (3)	5 (3)	17 (9)	2 (3)	4 (6)	6 (2)	7 (3)
Fatigue	4 (3)	6 (4)	7 (5)	2 (1)	9 (5)	8 (4)	5 (3)	4 (6)	7 (10)	11 (4)	7 (3)
Antidrug antibodies	2 (1)‡	3 (2)‡	2 (1)‡	1 (<1)‡	3 (2)‡	7 (4)‡	9 (5)‡	0	6 (9)	5 (2)‡	10 (4)‡

IV, Intravenous; SC, subcutaneous; URTI, upper respiratory tract infection.

*In the opinion of the investigator.

†Those reported in at least 5% of the patients in any study group.

‡No neutralizing antibodies were detected.

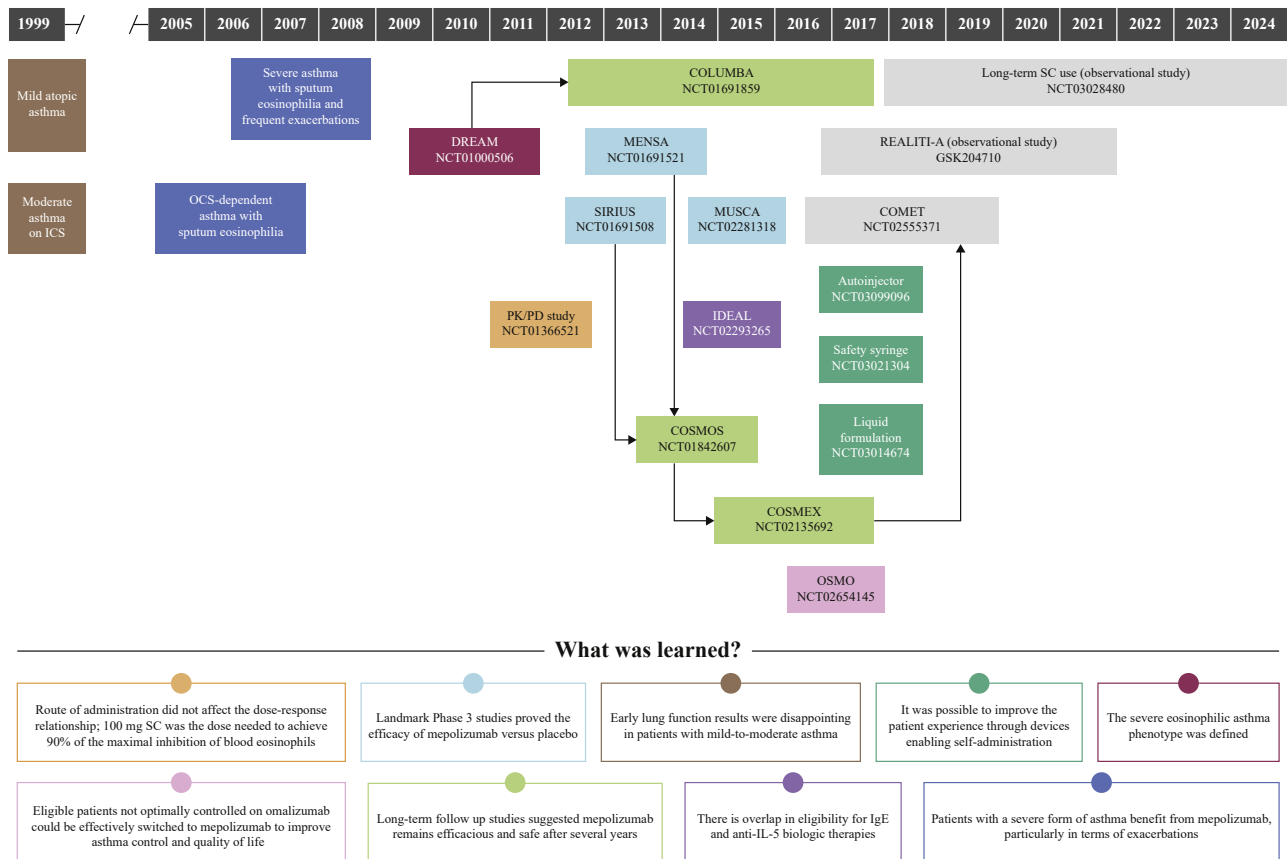


FIGURE 4. Key studies in the 20 years of clinical development with mepolizumab, and beyond. For individual inclusion and exclusion criteria see Table E2, available in this article's Online Repository at www.jaci-inpractice.org. ICS, Inhaled corticosteroid; OCS, oral corticosteroid; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous.

exacerbation rate remained low (0.93 events/year) in those who had participated in COSMOS or MENSA, and improvements in FEV₁ and ACQ-5 scores were maintained across the extension period.⁵⁸ In those patients who had a gap in their treatment of greater than 3 months between COSMOS and COSMEX, patients experienced a decrease in FEV₁ and an increase in ACQ-5 score. These data were consistent with the long-term safety study COLUMBA (NCT01691859).⁷³ The long-term efficacy of benralizumab has also been investigated in an open-label extension of the phase 3 studies. Improvements in exacerbation rates and lung function were maintained into the second year of treatment.⁷⁴ Similarly, initial improvements in lung function and asthma control seen during the phase 3 reslizumab studies were maintained for up to 2 years in an open-label extension study.⁷⁵

SAFETY

Overall, the anti-IL-5 agents have displayed safety profiles that are similar to placebo during their phase 3 development programs.^{30,34,36,38,42-45} In the DREAM, MENSA, SIRIUS, and MUSCA trials, mepolizumab demonstrated a consistent safety profile, broadly similar to placebo (Table II).^{30,34,36,38} The most frequently reported adverse events (AEs) with mepolizumab in these trials were nasopharyngitis and headache and the incidence of serious drug-related AEs was low ($\leq 1\%$). Similarly,

nasopharyngitis, headache, worsening asthma, and upper respiratory tract infection were among the most frequently reported AEs in the benralizumab and reslizumab trials, with serious drug-related AEs also remaining below 1%.⁴²⁻⁴⁵

The long-term safety of mepolizumab for up to 4.8 years has also been assessed in the COSMOS,⁷² COLUMBA,⁷³ and COSMEX⁵⁸ extension studies. They found that mepolizumab has a favorable long-term safety profile and is well tolerated,^{58,72,73} with a safety profile consistent with previous randomized controlled trials comparing mepolizumab versus placebo.^{30,34,36,38} In addition, a low proportion of patients in COSMEX and COLUMBA reported antidrug antibodies after baseline (2% and 8%, respectively, with no neutralizing antibodies detected) and zero patients reported anaphylaxis in COLUMBA or COSMEX.^{58,73} The safety and efficacy results reported in these 3 trials also represent the longest reported follow-up for patients receiving any anti-IL-5/IL-5 receptor therapies. Benralizumab and reslizumab have also been shown to be well tolerated for up to 2 years, with a safety profile consistent with that shown in randomized controlled trials.^{74,76}

FUTURE DIRECTIONS

As more data are collected on the different anti-IL-5 therapies, further questions will be answered regarding their long-term clinical effects and treatment choice. Although the effect of

mepolizumab in a relatively long-term timeframe (up to 4.8 years) is known, particularly compared with the timeframe over which the efficacy of other recently approved asthma biologics is known, further data will be collected and analyzed to address outstanding queries. These include the question of whether anti-IL-5 therapy and biologic therapies in general are disease modifying in asthma.

It was previously considered that anti-IL-5 therapies could be disease modifying through prevention of airway remodeling, given that treatment with mepolizumab resulted in reduced expression of extracellular matrix proteins in the airway reticular basement membrane.⁷⁷ This was supported by the determination that mepolizumab 750 mg IV monthly for 50 weeks reduced computerized tomography-assessed airway wall area.²⁸ However, a further report demonstrated increased asthma symptoms after discontinuation of mepolizumab in the absence of changes in other clinical measures or worsening eosinophilic airway inflammation,⁷⁸ similar to the effect after cessation of long-term omalizumab treatment.⁷⁹ This suggested a need for maintenance suppression of eosinophilic airway inflammation in patients with severe eosinophilic asthma and recurrent exacerbations.⁸⁰ Although these did not support a residual disease-modifying effect of mepolizumab, they further confirmed the relationship between blood eosinophil counts and clinical effects. Indeed, exacerbations experienced by patients currently on mepolizumab treatment have been shown to be associated with lower sputum eosinophils and less severe symptoms than exacerbations in patients receiving placebo treatment,⁸¹ further supporting the association between reduced eosinophil counts and clinical effects and highlighting the importance of targeted therapies. Additional studies, such as COMET (NCT02555371), which is designed to determine whether patients who halt treatment after at least 3 years of mepolizumab use continue to maintain clinical benefit, should help to clarify whether maintenance suppression of eosinophilic airway inflammation is required.

Other observational trials will reveal more information on the long-term effect of anti-IL-5 in real-world settings. These include a prospective, long-term observational study of mepolizumab SC in 1000 patients with up to 2 years of follow-up after at least 52 weeks of treatment at the investigator's discretion (NCT03028480). In addition, the prospective, real-world REALITI-A study of mepolizumab in patients in routine clinical practice is also being carried out. Indeed, an initial 12-month analysis of patients in REALITI-A has indicated that the effectiveness of mepolizumab is similar in real-world and clinical trial settings.⁸² Other outstanding questions include whether anti-IL-5/IL-5 receptor therapy use decreases the use of other controller medications and characterizing the efficacy of anti-IL-5/IL-5 receptor therapy in patients who have the best responses, that is, how long do these patients continue to experience low rates of exacerbations?

A further important area of investigation is the evolving use of a ready-to-use prefilled syringe or prefilled autoinjector (AI) in asthma, which allows self-administration of anti-IL-5 therapy at home. Studies with mepolizumab have shown this to be a viable, cost-effective alternative to the current reconstituted product, with a similar PK profile.⁸³⁻⁸⁶ Currently, both mepolizumab and benralizumab can be administered by patients/caregivers at home using an AI.^{4,13,87}

CONCLUSION

The development of mepolizumab is an example of a clinical development process founded on solid scientific principles (Figure 4), which helped to further knowledge of the role of eosinophils in asthma. Thanks to a thorough understanding of asthma disease pathobiology, it is now clear that patients with severe eosinophilic asthma with recurrent exacerbations form the appropriate target population for mepolizumab, allowing for an unmet need in this population to be fulfilled. The clinical development pathway of mepolizumab has a wider importance as it set the scene for the successful clinical development of other biologic agents, such as benralizumab, dupilumab, and reslizumab, and led to the introduction of clinically important prognostic and predictive biomarkers.⁹ We predict that targeting mechanistic pathways (treatable traits) rather than arbitrary physiologically defined disease entities will become the standard approach to new drug development in airways disease.

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TABLE E1. Clinical improvements in patient subgroups at Week 32 after switch from omalizumab to mepolizumab^{E1-E4}

	Omalizumab duration of use			Omalizumab prior treatment regimen		Comorbid conditions						Baseline blood eosinophil count			
						Nasal polyps		Aspirin/NSAID intolerance		GERD					
	<1.5 y (n = 50)	1.5 to <4 y (n = 51)	≥4 y (n = 43)	Every 2 wk (n = 75)	Every 4 wk (n = 69)	Yes (n = 20)	No (n = 125)	Yes (n = 17)	No (n = 128)	Yes (n = 54)	No (n = 91)	≥150 cells/μL (n = 120)	≥300 cells/μL (n = 77)	≥400 cells/μL (n = 61)	≥500 cells/μL (n = 52)
ACQ-5 score improvements, LS mean change (SE)	-1.40 (0.180)	-1.65 (0.181)	-1.31 (0.200)	-1.33 (0.144)	-1.61 (0.159)	-1.86 (0.223)	-1.38 (0.119)	-1.68 (0.262)	-1.42 (0.116)	-1.39 (0.166)	-1.48 (0.140)	-1.46 (0.120)	-1.69 (0.143)	-1.77 (0.137)	-1.76 (0.149)
SGRQ total score improvements, LS mean change (SE)	—	—	—	-17.8 (2.29)	-20.1 (2.38)	-24.2 (4.62)	-18.1 (1.75)	-14.1 (4.59)	-19.6 (1.75)	-18.4 (2.37)	-19.2 (2.21)	-18.5 (1.87)	-22.7 (2.15)	-24.1 (2.42)	-24.7 (2.71)
Pre-bronchodilator FEV ₁ (mL), LS mean change (SE)	—	—	—	161 (54.6)	136 (58.9)	217 (118.9)	150 (43.3)	294 (117.9)	143 (43.3)	126 (67.6)	178 (51.2)	177 (45.8)	246 (49.0)	256 (54.5)	286 (56.5)
Exacerbation rate ratio* (95% CI)	—	—	—	0.32 (0.22, 0.46)	0.41 (0.29, 0.58)	0.38 (0.21, 0.69)	0.36 (0.27, 0.47)	0.56 (0.35, 0.89)	0.33 (0.24, 0.45)	0.28 (0.18, 0.43)	0.42 (0.31, 0.58)	—	—	—	—

ACQ, Asthma Control Questionnaire; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; GERD, gastroesophageal reflux disease; LS, least squares; NSAID, nonsteroidal anti-inflammatory drug; SE, standard error; SGRQ, St George's Respiratory Questionnaire.

*Ratio of the annualized rate (on-treatment/pretreatment), where pretreatment period (12 months before screening) is compared with the 32-week study period (between first dose and study conclusion).

(continued)

(continued)

TABLE E2. (Continued)

	Mild atopic asthma ^{E5}	Moderate asthma on ICS ^{E6}	OCS-dependent asthma with sputum eosinophilia ^{E7}	Severe asthma with sputum eosinophilia and frequent exacerbations ^{E8}	DREAM ^{E9}	PK/PD study ^{E10}	SIRIUS ^{E11}	MENSA ^{E12}	COLUMBA ^{E13}	COSMOS ^{E14}	IDEAL ^{E15}	MUSCA ^{E16}	COSMEX ^{E17}	OSMO ^{E18}	COMET	REALITI-A	Retrospective observational study ^{E19}	Autoinjector ^{E20}	Safety syringe ^{E21}	Liquid formulation ^{E22}
Positive neutralizing antibody status and/or hypersensitivity reaction related to mepolizumab leading to study withdrawal and/or SAE possibly related to mepolizumab									↙	↙										

ATS, American Thoracic Society; ERS, European Respiratory Society; *FeNO*, fractional exhaled nitric oxide; *FEV₁*, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; NHLBI, National Heart, Lung, and Blood Institute; OCS, oral corticosteroid; *PC₂₀*, provocative concentration of inhaled methacholine needed to reduce FEV₁ by 20%; PD, pharmacodynamic; PEF, peak expiratory flow; PK, pharmacokinetic; SABA, short-acting β_2 -agonist; SAE, serious adverse event; SCS, systemic corticosteroid; URTI, upper respiratory tract infection.

*Or blood eosinophil count ≥ 150 cells/ μ L at screening/ ≥ 300 cells/ μ L in the prior year, high-dose ICS plus an additional controller and ≥ 1 asthma exacerbation requiring SCS.

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