Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma

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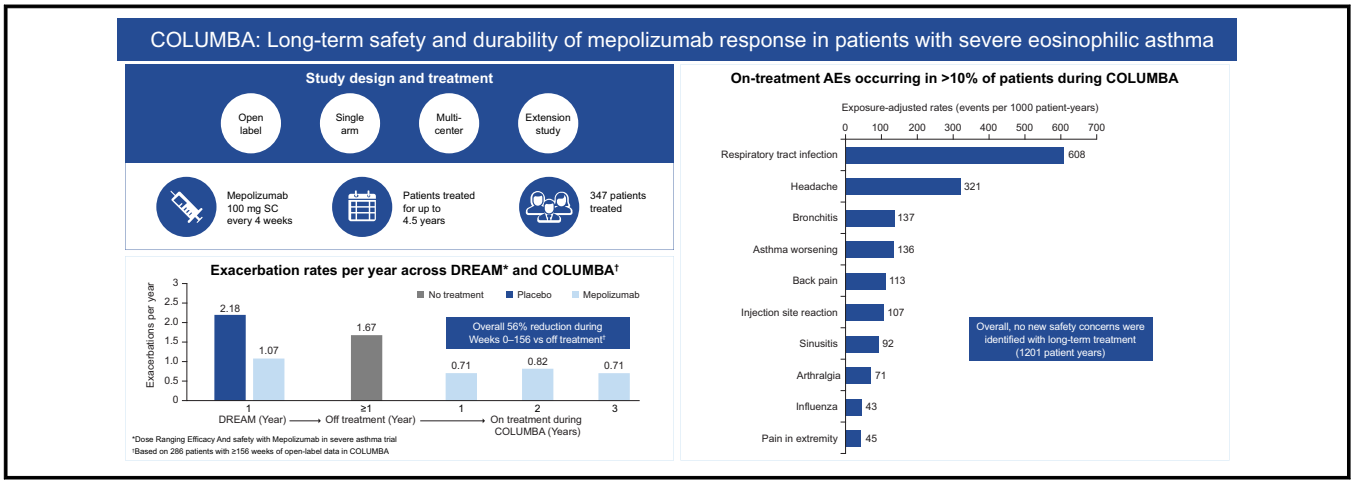
GRAPHICAL ABSTRACT



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

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Background: Mepolizumab has demonstrated favorable safety and efficacy profiles in placebo-controlled trials of 12 months' duration or less; however, long-term data are lacking.
Objective: We sought to evaluate the long-term safety and efficacy of mepolizumab in patients with severe eosinophilic asthma (SEA).
Methods: COLUMBA (Open-label Long Term Extension Safety Study of Mepolizumab in Asthmatic Subjects, NCT01691859) was an open-label extension study in patients with SEA previously enrolled in DREAM (Dose Ranging Efficacy And Safety With Mepolizumab in Severe Asthma, NCT01000506). Patients received 100 mg of subcutaneous mepolizumab every 4 weeks plus standard of care until a protocol-defined stopping criterion was met. Safety end points included frequency of adverse events (AEs), serious AEs, and AEs of special interest. Efficacy end points included annualized exacerbation rates, changes from baseline in Asthma Control Questionnaire 5 scores, and blood eosinophil counts. Immunogenicity was also assessed.
Results: Overall, 347 patients were enrolled for an average of 3.5 years (maximum, 4.5 years; total exposure, 1201 patient-years). On-treatment AEs were reported in 94% of patients (exposure-adjusted rate, 3688 events/1000 patient-years). The most frequently reported on-treatment AEs were respiratory tract infection, headache, bronchitis, and asthma worsening. Seventy-nine (23%) patients experienced 1 or more on-treatment serious AEs; there were 6 deaths, none of which were assessed as related to mepolizumab. For patients with 156 weeks or greater enrollment, the exacerbation rate was 0.74 events/y (weeks 0–156), a 56% reduction from the off-treatment period between DREAM and COLUMBA. For all patients, at the first postbaseline assessment, the mean Asthma Control Questionnaire 5 score was reduced by 0.47 points, and blood eosinophil counts were reduced by 78%, with similar improvements maintained throughout the study. The immunogenicity profile (8% anti-drug antibodies) was consistent with previous studies.
Conclusion: These data support the long-term safety and efficacy of mepolizumab in patients with SEA. (J Allergy Clin Immunol 2019;143:1742-51.)

Key words: *Mepolizumab, severe eosinophilic asthma, long-term safety, extension study*

Abbreviations used

ACQ-5:	Asthma Control Questionnaire 5
ADA:	Anti-drug antibody
AE:	Adverse event
AESI:	Adverse event of special interest
COLUMBA:	Open-label Long Term Extension Safety Study of Mepolizumab in Asthmatic Subjects, NCT01691859
COSMOS:	A Study to Determine Long-term Safety of Mepolizumab in Asthmatic Subjects, NCT01842607
DREAM:	Dose Ranging Efficacy And Safety With Mepolizumab in Severe Asthma, NCT01000506
EXCELS:	A Study of Xolair to Evaluate Effectiveness and Long-Term Safety in Patients With Moderate to Severe Asthma, NCT00252135
MENSA:	Efficacy and Safety Study of Mepolizumab Adjunctive Therapy in Subjects With Severe Uncontrolled Refractory Asthma, NCT01691521
MUSCA:	Efficacy and Safety Study of Mepolizumab Adjunctive Therapy in Participants With Severe Eosinophilic Asthma on Markers of Asthma Control, NCT02281318
NAb:	Neutralizing drug antibody
SAE:	Serious adverse event
SEA:	Severe eosinophilic asthma
SIRIUS:	Mepolizumab Steroid-Sparing Study in Subjects With Severe Refractory Asthma, NCT01691508

Severe asthma is a heterogeneous condition in which patients present with different clinical and physiologic characteristics and display differing treatment responses.[1,2] The addition of biologics to standard-of-care asthma therapy has introduced a more personalized treatment approach for patients with severe asthma,[3,4] providing direct benefit in reducing exacerbations and improving other markers of asthma control. However, there are limited data evaluating the long-term safety of these biologics and the durability of the treatment response.

Mepolizumab, an anti–IL-5 humanized mAb, is recommended as a step 5 therapy option for patients with severe eosinophilic asthma (SEA).[3] The efficacy of mepolizumab in patients with SEA has been demonstrated, with strong and consistent exacerbation reductions in 4 randomized placebo-controlled trials: DREAM (Dose Ranging Efficacy And Safety With Mepolizumab in Severe Asthma, NCT01000506),[5] MENSA (Efficacy and Safety Study of Mepolizumab Adjunctive Therapy in Subjects With Severe Uncontrolled Refractory Asthma, NCT01691521),[6] SIRIUS (Mepolizumab Steroid-Sparing Study in Subjects With Severe Refractory Asthma, NCT01691508),[7] and MUSCA (Efficacy and Safety Study of Mepolizumab Adjunctive Therapy in Participants With Severe Eosinophilic Asthma on Markers of Asthma Control, NCT02281318).[8] In comparison with placebo in these trials, mepolizumab also improved quality of life, asthma control, and lung function.[5-8] In addition, during SIRIUS, patients treated with mepolizumab were significantly more likely to achieve a 50% or greater reduction in daily oral glucocorticoid dose than patients treated with placebo.[7] In these studies treatment with mepolizumab was associated with an average reduction in peripheral blood eosinophil counts to 40 cells/μL.[4]

In further support of the established efficacy of mepolizumab in patients with SEA, mepolizumab has demonstrated a consistent safety profile in all randomized placebo-controlled trials.[5-8] Additionally, in COSMOS (A Study to Determine Long-term Safety of Mepolizumab in Asthmatic Subjects, NCT01842607), a 52-week open-label extension study of MENSA and SIRIUS, mepolizumab had a favorable long-term safety profile, with no increase in the rate of adverse events (AEs) over the study period or compared with previous placebo-controlled trials.[9]

Although mepolizumab has demonstrated a favorable safety profile in placebo-controlled trials of up to 12 months' duration and in an open-label extension study, long-term safety data in patients with SEA beyond 1.5 years are lacking. Here we report the results of an open-label, long-term extension in patients who participated in the DREAM study. The primary objective was to describe the safety profile of mepolizumab in patients receiving long-term treatment. The effects of mepolizumab on a range of clinical markers of asthma control were also assessed.

METHODS

Study design

COLUMBA (GlaxoSmithKline ID MEA115666; NCT01691859)[10] was a multicenter, open-label, long-term safety study conducted in patients who had previously participated in the DREAM study (GlaxoSmithKline ID MEA112997).[5] In brief, DREAM was a randomized, double-blind, placebo-controlled trial of mepolizumab in patients with SEA (aged ≥12 years) who were randomized to receive intravenous mepolizumab at 75, 250, or 750 mg or placebo every 4 weeks for 52 weeks.

Patients were invited to participate in COLUMBA 12 to 28 months after they completed the DREAM study. This study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice, applicable country-specific requirements, and ethical principles outlined in the Declaration of Helsinki. All patients provided written informed consent before any study-related activities.

Patients

To be eligible for inclusion in COLUMBA, patients had to have been randomized and received at least 2 doses of treatment (mepolizumab or placebo) in the DREAM study[5] and to have been receiving an asthma controller medication for 12 or more weeks before enrollment in this study.

Patients were excluded from this study if they experienced any of the following during or since participation in the DREAM study: a positive neutralizing drug antibody (NAb) status based on the last sample, a report of a hypersensitivity reaction (aside from injection-site reactions) assessed as related to mepolizumab by the investigator that led to withdrawal, a serious adverse event (SAE) assessed as possibly related to mepolizumab by the investigator, or a clinically significant change in health status that in the opinion of the investigator would make the patient unsuitable for participation in this long-term study. Further exclusion criteria are detailed in the Methods section in this article's Online Repository at www.jacionline.org.

Treatments

During COLUMBA, all patients received 100 mg of mepolizumab administered subcutaneously every 4 weeks, regardless of previous treatment regimen, until a protocol-defined stopping criterion was met (see the Methods section in this article's Online Repository). Patients continued to receive standard-of-care asthma therapy for the duration of the study, which could be adjusted at the discretion of their physicians.

End points

Safety end points. The primary safety end point was the frequency of all AEs, SAEs, and adverse events of special interest (AESIs). All AESIs are listed within the Methods section in this article's Online Repository. AEs were recorded on a worksheet by patients and documented by study staff at each visit. Deaths from any cause and selected cardiovascular events (see the Methods section in this article's Online Repository) were adjudicated by a Clinical Endpoint Committee.

Secondary safety end points included 12-lead electrocardiograms, which were assessed at screening every 24 weeks throughout the study and 4 weeks after the last dose, as well as vital signs and clinical laboratory assessments, which were monitored throughout the study.

Efficacy end points. Exacerbations were recorded on a worksheet by patients and documented by study staff at each visit. The definition of an exacerbation is detailed within the Methods section in this article's Online Repository. The Asthma Control Questionnaire 5 (ACQ-5) was used to assess asthma control at baseline and every 12 weeks throughout the study. Spirometry, assessed as FEV_1, was conducted at baseline and every 12 to 24 weeks throughout the study. Patients were asked to withhold short-acting β_2-agonists for 6 or more hours and long-acting β_2-agonists for 12 or more hours before the clinic visit, if possible. Blood eosinophil counts were assessed at baseline and at specified times throughout the study.

Immunogenicity end points. Immunogenicity testing for the presence of anti-drug antibodies (ADAs), which were defined as any antibody isotype directed against mepolizumab, was performed in blood by using electrochemiluminescence. Samples testing positive for ADAs were further tested for the presence of NAbs.

Statistical analysis

No sample size was calculated; the study population was determined by the number of patients randomized in the DREAM study who were eligible for and willing to participate in COLUMBA. All analyses were performed by using the as-treated population, which was defined as all patients who received at least 1 dose of open-label mepolizumab. All end points were summarized by using appropriate descriptive statistics (means/geometric means, medians, standard deviations, and ranges).

AEs were summarized by using the Medical Dictionary for Regulatory Activities Primary System Organ Class and Preferred Terms. Exposure-adjusted rates of AEs per 1000 patient-years were calculated. The annualized rate of on-treatment exacerbations for each study period was analyzed by using a negative binomial generalized linear model with logarithm of time as an offset variable, from which the estimated rate per year and associated 95% CIs were calculated. Asthma control and spirometric end points were assessed as changes from baseline. For blood eosinophil counts, ratio to baseline was summarized by visit; if a result of zero was recorded, a small value (ie, half the minimum nonzero result) was imputed before log-transformation. All statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC).

Post hoc subgroup analyses were conducted to assess the annualized on-treatment exacerbation rate by baseline blood eosinophil count by using the following subgroups: 150 cells/μL or greater, 300 cells/μL or greater, 400 cells/μL or greater, and 500 cells/μL or greater. Additionally, AEs, SAEs, exacerbation rates, and ACQ-5 scores were assessed *post hoc* in patients with early-onset (<33 years of age) and late-onset (≥33 years of age) asthma and in patients with and without chronic rhinosinusitis present at screening.

RESULTS

Patient population

This study was conducted between September 28, 2012, and May 31, 2017, in 65 centers across 13 countries (see the Methods section in this article's Online Repository). Overall, 362 patients were enrolled in the study, and 347 were included in the as-treated population, corresponding to 56% of the DREAM intent-to-treat population. An overview of patient flow through the study is shown in Fig 1. Most patients (n = 221 [64%]) remained in the study until mepolizumab became commercially available in their country, and 50 (14%) patients in countries awaiting regulatory or reimbursement approval remained in the study at closure. Nineteen (5%) patients withdrew because of an AE; the only AE resulting in more than 1 patient withdrawal was asthma worsening (n = 3 [<1%]; see Table E1 in this article's Online Repository at www.jacionline.org). A summary of time to study discontinuation is presented in Fig 2; this reflects the staged study closure as mepolizumab became commercially available for prescription in each participating country.

Patients' demographic and clinical characteristics at baseline are summarized in Table I. Patients had a mean age of 52.2 years, and 65% were female. The median period from completion of DREAM to enrollment in COLUMBA was 17.8 months (range, 12–28 months), and patients were evenly distributed from each of the 4 treatment arms of the DREAM study (22% to 28% across groups). Over the COLUMBA study period, the mean duration of treatment was 3.5 years (range, 4 weeks to 4.5 years); exposure to mepolizumab amounted to 1201 patient-years.

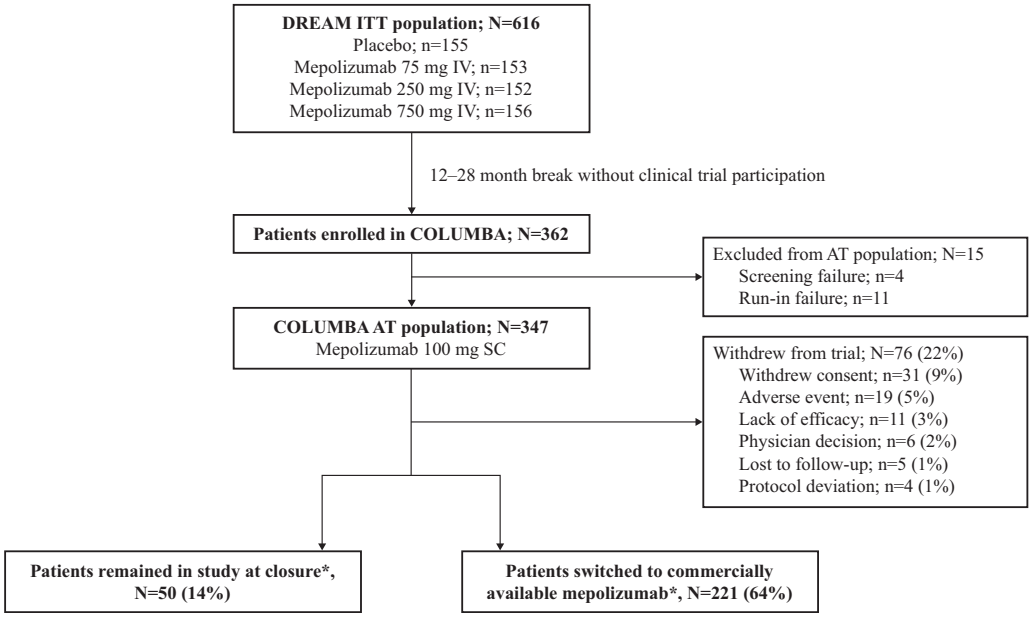

FIG 1. Patient flow through the COLUMBA study. *After completion of COLUMBA, patients could enter a further mepolizumab study (201810 or 201956) or choose to receive mepolizumab commercially outside of a clinical trial. *ITT*, Intent-to-treat; *IV*, intravenous; *SC*, subcutaneous.

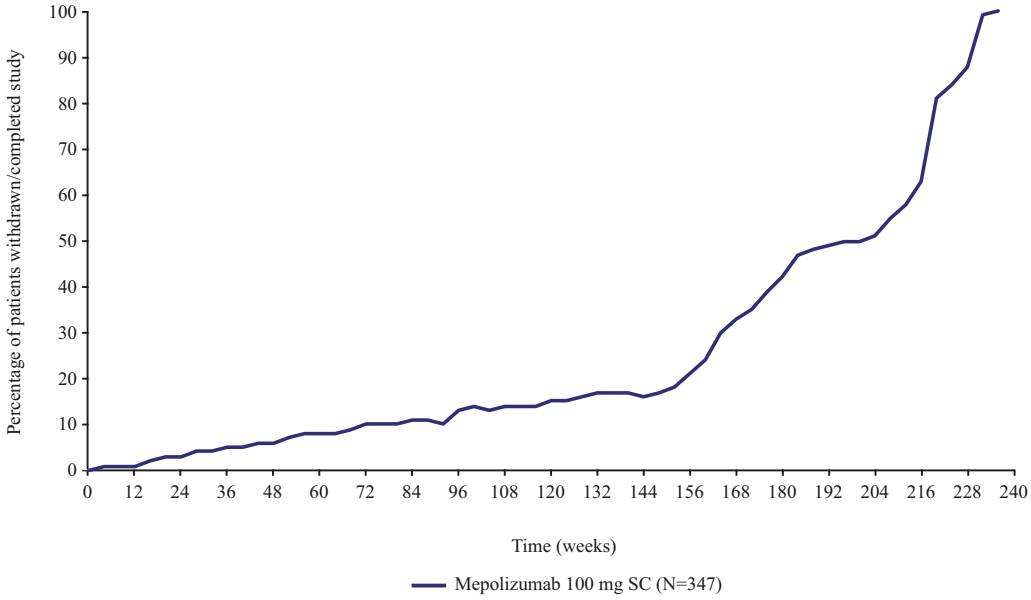

FIG 2. Time to study cessation. Study closure was conducted in a staged manner as mepolizumab became commercially available for prescription in each participating country. *SC*, Subcutaneous.

Safety end points

Overall, 326 (94%) patients experienced at least 1 on-treatment AE, resulting in an exposure-adjusted rate of 3688 events per 1000 patient-years. Respiratory tract infection (n = 231 [67%]), headache (n = 99 [29%]), asthma worsening (n = 94 [27%]), and bronchitis (n = 73 [21%]) were the most commonly reported on-treatment AEs (Fig 3, *A*). Ninety-seven (28%) patients reported an on-treatment AE that was assessed by the investigator as related to the study treatment. The only on-treatment drug-related AEs reported with an incidence 3% or greater were injection-site reactions (12%; exposure-adjusted rate, 103 events per 1000 patient-years) and headache (4%; exposure-adjusted rate, 30 events per 1000 patient-years).

A total of 159 SAEs were reported in 82 (24%) patients during the conduct of this study, with 79 (23%) patients experiencing any on-treatment SAE (Table II).[11,12] On-treatment SAEs reported in more than 1 patient are summarized in Fig 3, *B*. Six fatalities were reported: 1 patient experienced sudden death; 1 patient died of respiratory arrest; 1 patient died of morbid obesity, chronic asthma, and sleep apnea; 1 patient died of myocardial infarction;

TABLE I. Baseline demographic and clinical characteristics (as-treated population)

Characteristic	Mepolizumab, 100 mg SC (n = 347)
Age (y), mean (SD)	52.2 (10.73)
Sex, female, no. (%)	224 (65)
Race, no. (%)	
White	318 (92)
Asian	18 (5)
Other	11 (3)
Non-Hispanic, no. (%)	306 (88)
Body mass index (kg/m^2), mean (SD)	28.6 (6.10)
Comorbidities of interest, no. (%)	
Allergic rhinitis or hay fever	165 (48)
Chronic rhinosinusitis	41 (12)
Nasal polyposis	24 (7)
Duration of disease (y), mean (SD)	21.4 (14.22)
Age of onset of disease (y), median (range)	33 (0-66)
Lung function tests at baseline	
Prebronchodilator FEV_1 (mL), mean (SD)	1811 (696.2)
Prebronchodilator % predicted normal FEV_1, mean (SD)	60.1 (18.89)
Prebronchodilator FEV1/FVC ratio, mean (SD)	0.62 (0.121)
ACQ-5* score at baseline	n = 346
Mean (SD)	2.21 (1.169)
Blood eosinophil count at baseline (cells/μL)	n = 337
Geometric mean (SD logs)	240 (1.016)
Median (minimum-maximum)	270 (0-1600)
Concurrent therapy, no. (%)	
ICS†	347 (100)
LABA‡	339 (98)
SABA	315 (91)
Xanthine	75 (22)
LTRA	63 (18)
LAMA	51 (15)
Maintenance OCS use at baseline, no. (%)	90 (26)
Period since completion of DREAM (mo), median (range)	17.8 (12-28)
Exacerbations since completion of DREAM	
Exacerbations, mean (SD)	2.7 (4.74)
No. of patients to experience ≥1 event (%)	280 (81)
Exacerbations requiring ED/hospitalization, mean (SD)	0.4 (0.83)
No. of patients to experience ≥1 event (%)	75 (22)
Exacerbations requiring hospitalization, mean (SD)	0.2 (0.59)
No. of patients to experience ≥1 event (%)	55 (16)
Annualized rate of exacerbations since completion of DREAM, mean (SD)	
As-treated population	1.74 (2.94)
Baseline blood eosinophil count subgroup	
≥150 cells/μL (n = 243)	1.64 (1.76)
≥300 cells/μL (n = 153)	1.69 (1.89)
≥400 cells/μL (n = 106)	1.69 (1.94)
≥500 cells/μL (n = 80)	1.69 (1.86)

ED, Emergency department; *FVC*, forced vital capacity; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *LTRA*, long-acting leukotriene receptor antagonist; *OCS*, oral corticosteroids; *SABA*, short-acting β_2-agonist; *SC*, subcutaneous.

*Scale scores: 0, no impairment; 6, maximum impairment.

†During the DREAM study, patients required 880 μg/d fluticasone propionate or greater; however, ICS doses might have been reduced after completion of the study.

‡LABA was provided concomitant with ICS, as per standard-of-case guidelines.

1 patient died of acute heart failure; and 1 patient died of a severe asthma exacerbation. The patient who died of a severe asthma exacerbation had a disease duration of 12.5 years, a baseline blood eosinophil count of 30 cells/μL, and a history of sinusitis, which was resolved before entry into DREAM. This death was not adjudicated because the information for adjudication was not available. No fatal SAEs were assessed as possibly related to study treatment.

A *post hoc* analysis of AEs by age of asthma onset was also performed. Patients were defined as having early- and late-onset asthma based on the median age of asthma diagnosis in the study (33 years). Back pain, arthralgia, and pain in the extremities were more frequently reported in the late-onset group (those with diagnosis at ≥33 years, n = 174) compared with the early-onset group (those with diagnosis at <33 years, n = 173; see Table E2 in this article's Online Repository at www.jacionline.org). In addition, the frequency of reported bronchitis was greater in the early-onset group compared with the late-onset group. Overall, the proportion of patients reporting SAEs was similar between the 2 groups (see Fig E1 in this article's Online Repository at www.jacionline.org).

As expected, respiratory tract infections were reported more frequently in patients who had chronic rhinosinusitis at screening. In addition, a slightly higher proportion of patients with chronic rhinosinusitis at screening reported worsening of their asthma symptoms (n = 13 [32%]) compared with those who did not have chronic rhinosinusitis at screening (n = 81 [26%]; see Table E3 in this article's Online Repository at www.jacionline.org).

All on-treatment AESIs are summarized in Table II. Eight (2%) patients experienced allergic/hypersensitivity systemic reactions, and 1 (<1%) patient experienced a nonallergic systemic reaction. Investigators were requested to assess AEs they considered systemic reactions against Sampson's diagnostic criteria for anaphylaxis.[11] There were no reports of mepolizumab-related anaphylaxis. Twenty-four (7%) patients experienced an on-treatment opportunistic infection, of whom 8 (2%) patients experienced herpes zoster infection (17 events per 1000 patient-years); 1 event was reported as serious. No parasitic infections were reported. Six (2%) patients reported malignancies while receiving treatment: 3 (<1%) patients had basal cell carcinoma (5.8 events per 1000 patient-years), 2 (<1%) patients had prostate cancer (1.7 events per 1000 patient-years), and 1 (<1%) patient had breast cancer (0.83 events per 1000 patient-years).

There were no reports of clinically significant changes in electrocardiographic findings or laboratory data, and vital signs remained stable throughout the study (data not shown).

Efficacy end points

Over the study period, the annualized rate of on-treatment exacerbations across all enrolled patients was 0.68 events/y (95% CI, 0.60-0.78 events/y), representing a 61% reduction from the off-treatment period between DREAM and COLUMBA (1.74 events/y). For patients with 156 weeks enrollment or greater in COLUMBA, the mean annualized rate of exacerbations was 0.74 events/y for weeks 0 to 156, representing a 79% reduction from the 12 months before DREAM and a 56% reduction from the off-treatment period between DREAM and COLUMBA (Fig 4, *A*,

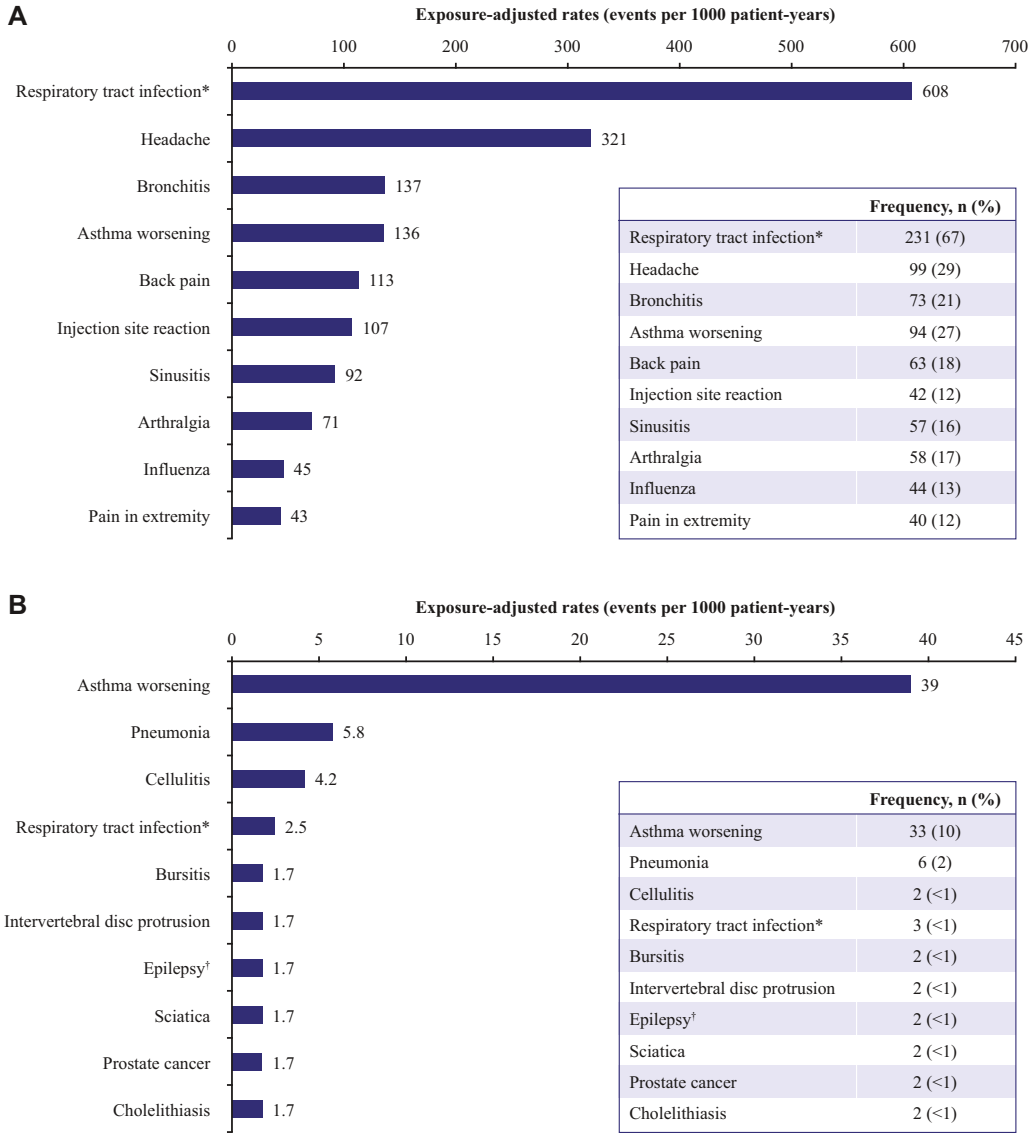

FIG 3. Summary of on-treatment AEs occurring in more than 10% of patients **(A)** and on-treatment SAEs occurring in more than 1 patient (as-treated population; **B**). *Respiratory tract infection encompasses all AEs reported as (1) viral upper respiratory tract infection; (2) upper respiratory tract infection; (3) respiratory tract infection; (4) lower respiratory tract infection; (5) respiratory tract infection, viral; (6) lower respiratory tract infection, viral; and (7) upper respiratory tract infection, bacterial. †One patient had a childhood history of epilepsy.

and see Table E4 in this article's Online Repository at www.jacionline.org). *Post hoc* analysis showed similar rates of on-treatment exacerbations for all baseline blood eosinophil count subgroups (see Fig E2 in this article's Online Repository at www.jacionline.org). In addition, similar annualized rates of on-treatment exacerbations were observed when patients were grouped by early (<33 years; 0.69 events/y [95% CI, 0.58-0.83 events/y]) or late (≥33 years; 0.67 events/y [95% CI, 0.55-0.82 events/y]) asthma onset. Consistent with the previously discussed subgroup analysis of AEs, *post hoc* analysis indicated marginally higher on-treatment exacerbation rates for patients with chronic rhinosinusitis at screening compared with those without chronic rhinosinusitis present (1.04 vs 0.69 events/y).

Improvements in asthma control were observed at the first postbaseline assessment (week 12), with a mean reduction from baseline in ACQ-5 score of 0.47 points. Similar improvement was maintained throughout the study, with the mean change in ACQ-5 score ranging from 0.40 points (week 188) to 0.66 points (week 124) and approximately 50% of patients achieving an improvement (decrease) in ACQ-5 score of 0.5 or more points at each postbaseline assessment (Fig 4, *B*). In addition, similar improvements in ACQ-5 scores were seen in patients who received a diagnosis of early-onset (<33 years of age) or late-onset (≥33 years of age) asthma. Mean reductions in ACQ-5 scores ranged from 0.58 (week 124) to 0.07 (week 228) points in the early-onset group and 0.75 (week 124) to 0.45 (week 188) points in the late-onset group.

TABLE II. Summary of on-treatment AEs (as-treated population)

	Mepolizumab, 100 mg SC (n = 347)
Any AE	326 (94)
Related to study treatment	97 (28)
Leading to withdrawal from the study	19 (5)
Any SAE	79 (23)
Related to study treatment	2 (<1)
Leading to withdrawal from the study	12 (3)
Fatal SAEs	6 (2)
AESIs	
Systemic reactions	9 (3)
Allergic/hypersensitivity reactions*	8 (2)
Nonallergic reactions†	1 (<1)
Anaphylaxis‡	0 (0)
Local injection-site reactions	42 (12)
All infections§	284 (82)
Serious infections	17 (5)
Opportunistic infections‖	24 (7)
Malignancies	6 (2)
Cardiac disorders¶	35 (10)
Serious cardiac, vascular, and thromboembolic events#	10 (3)
Serious ischemic events#	3 (<1)

Data are presented as numbers (percentages).
MedDRA, Medical Dictionary for Regulatory Activities; *SC*, subcutaneous; *SMQs*, standardized MedDRA queries.
*More than 1 allergic/hypersensitivity symptom could be described per event.
†Patient reported slight light headedness.
‡Considered by the investigator to represent a systemic reaction meeting Sampson's criteria for anaphylaxis.[11]
§All infections include all events in Infections and Infestations System Organ Class.
‖Identified based on published list of pathogens and/or presentations of specific pathogens to be considered as opportunistic infections in the setting of biologic therapy.[12]
¶Cardiac disorders includes all events in Cardiac Disorders System Organ Class.
#Identified through MedDRA SMQs.

Prebronchodilator FEV_1 values initially increased from baseline (mean, 1811 mL [SD, 696.2 mL]; percent predicted mean, 60.1% [SD, 18.9%]) to a mean of 1955 mL (SD, 728 mL) at week 24 (percent predicted mean, 65.0% [SD, 19.8%]) and gradually decreased over the remainder of the study period. At week 200, the mean prebronchodilator FEV_1 showed no clinically significant difference from baseline (1855 mL [SD, 660 mL]; percent predicted, 61.5% [SD, 17.1%]; Fig 4, *C*). Blood eosinophil counts were suppressed by 78% from a geometric mean of 240 cells/μL (SD logs, 1.016 cells/μL) at baseline to 50 cells/μL (SD logs, 0.951 cells/μL) at week 4 and remained suppressed throughout the study period (Fig 4, *D*).

Immunogenicity end points

Of the 341 patients tested at baseline, 1 patient had a positive ADA response. In DREAM this patient was ADA positive at baseline (titer value, 128) and subsequently received 250 mg of mepolizumab administered intravenously for 52 weeks. Within COLUMBA, the patient was ADA positive (titer value, 320) at baseline and all but 1 postbaseline visit (final visit titer value, 40).

At any time after baseline, 27 (8%) of 346 patients had positive ADA test results. Titer values after baseline were low for all patients with positive results (≤160; median, 32), and the presence of ADAs was transient in the majority of the ADA-positive patients (20/27). All samples were negative for NAbs.

DISCUSSION

This is the first study to report data evaluating the long-term durability and safety of the anti–IL-5 biologic mepolizumab in patients with SEA. The observed safety and immunogenicity profile of long-term subcutaneous mepolizumab treatment was similar to that seen in previous randomized placebo-controlled trials of mepolizumab with intravenous and subcutaneous administration and the COSMOS 52-week extension study.[5-8,13] The COLUMBA study had a substantially longer duration of up to 4.5 years compared with 12 months (plus the associated exposures from the original studies) for the COSMOS extension study.[9] Tolerability and immunogenicity are more meaningfully characterized over an extended period of time, providing a more comprehensive assessment of safety outcomes. In addition, patients were re-exposed to mepolizumab after a drug holiday, which was not the case in the COSMOS study.

Overall, no new safety concerns were identified in this study after long-term exposure. As reported previously,[14] cessation of mepolizumab at the end of the DREAM study led to a general decrease in patients' disease status, with increased blood eosinophil counts and exacerbations reported in the time between DREAM and COLUMBA. However, this extended interruption of mepolizumab dosing had no negative effect on the safety and efficacy of mepolizumab after treatment resumed. Results from this study strengthen the safety profile for mepolizumab in patients with severe asthma.

The most commonly reported AEs were respiratory tract infections and headaches, and the worsening or exacerbation of asthma was the most frequent SAE observed. The high frequency of respiratory tract infections is not uncommon in this type of patient. Of note, the rate of pneumonia was low (10.8 events/1000 patient-years). These data are in line with those observed in the COSMOS extension study, in which nasopharyngitis and upper respiratory tract infections were the most frequent AEs and worsening or exacerbation of asthma was the most frequent SAE. The rate of pneumonia was also found to be low (11.2 events/1000 patient-years).[9] Exposure-adjusted rates of headache among those treated with mepolizumab were found to be similar to those observed previously in patients while receiving placebo. In the original mepolizumab asthma registration studies,[5-7] headache was reported in placebo-treated patients with a rate of 647.8 events/1000 patient-years and 853.9 events/1000 patient-years in patients receiving mepolizumab. This compares with lower rates of 340.4 and 321.34 in mepolizumab-treated patients within the COSMOS and COLUMBA studies, respectively.

Six deaths were reported during the study after 1201 patient-years of exposure to mepolizumab, all of which were considered unrelated to mepolizumab treatment by the investigator. This rate is similar to rates in the treatment and placebo arms of the original mepolizumab asthma registration studies,[5-7] in which 3 deaths were reported after 687 patient-years of exposure to mepolizumab, and 2 deaths were reported after 284 patient-years of exposure to placebo. Finally, the number of cancers observed in the study population was similar to age- and sex-adjusted incidence rates from the Surveillance Epidemiology and End Results Registry in the United States.[15] Incidence rates of prostate and breast

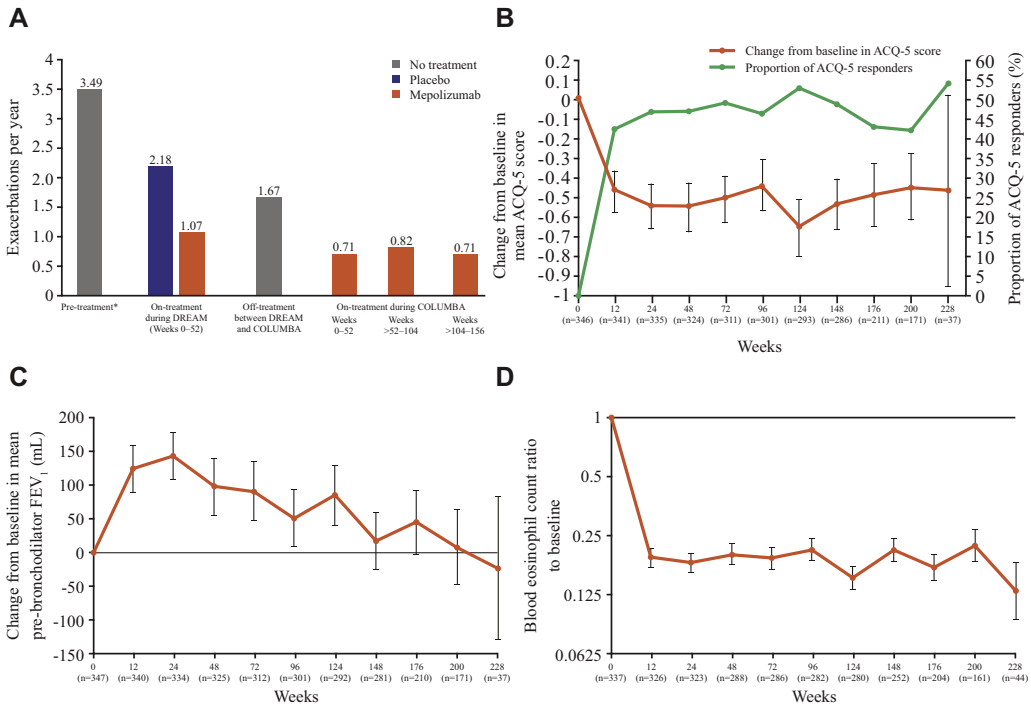

FIG 4. Summary of efficacy end points. **A,** Exacerbation rate per year across DREAM and COLUMBA. A total of 286 patients with 156 weeks or more of open-label data in COLUMBA are summarized (DREAM: placebo, n = 62; mepolizumab, n = 224). **B,** ACQ-5 score change from baseline. **C,** Prebronchodilator FEV_1 change from baseline. **D,** Blood eosinophil geometric mean ratio to baseline. Pretreatment refers to the 12 months before enrollment in DREAM. ACQ-5 responders were defined as patients with a reduction in ACQ-5 score of 0.5 points or more from baseline. *Vertical bars* show 95% CIs. Minimum clinically important difference: ACQ-5, 0.5 points; FEV_1, 100 mL.

cancers in this study were 1.7 and 0.83 events per 1000 patient-years, respectively, compared with 1.5 and 0.67 events per patient-years in the Surveillance Epidemiology and End Results Registry for 2007–2011.[16,17]

Immunogenicity findings were consistent with previous studies of mepolizumab, including the COSMOS extension study.[9] All samples were negative for NAbs. Positive ADA samples were infrequent, and in most cases positive titers were low and transient, with no suggestion of increased immunogenicity with treatment duration. The interruption in mepolizumab administration did not lead to greater immunogenicity for patients who previously received intravenous mepolizumab in the DREAM study, and there was no indication of a relationship between the frequency of AEs or hypersensitivity reactions and the presence or absence of ADAs.

Eosinophil count was used as a marker of pharmacodynamic response to mepolizumab. The magnitude of eosinophil suppression was consistent with that measured in previous mepolizumab studies.[5-8] Importantly, this study demonstrated the long-term durability of this pharmacodynamic effect and provided no evidence for tolerance to mepolizumab after re-exposure or long-term treatment.

Results from this study also demonstrate the durability of mepolizumab treatment response on various clinical parameters, including exacerbations, asthma control, and lung function. Most importantly, there was a sustained improvement in the rate of clinically significant exacerbations throughout the study period, with 33% of patients not experiencing an exacerbation during the long-term follow-up period. There were also sustained improvements in asthma control, with approximately 50% of patients achieving the minimum clinically important difference of 0.5 points at each postbaseline assessment.[18] It is worth noting that patients included in this study have more severe asthma than those included in the original validation populations for the ACQ-5.[18] As such, a clinically meaningful difference in asthma control might be experienced even if the reduction in ACQ-5 score reported is less than 0.5 points. Although in the overall population we observed consistent durability of clinical response, some patients might not respond fully or maintain the same level of response over time. There are limited data to understand clearly the mechanisms implicated in a potential loss of efficacy among biologics in the respiratory space. One report[19] indicates that we need to characterize these patients carefully in terms of comorbid conditions, environmental triggers, and non–type 2 inflammation, while also ensuring that they remain adherent to their baseline controller medication.

Initial improvements observed in lung function were consistent with those observed in previous mepolizumab studies.[5-8] This improvement gradually decreased to approximately baseline values at week 200, demonstrating a stabilization of the effect of the disease on lung function over the course of the study period. It has previously been demonstrated that some patients with severe asthma and frequent or severe exacerbations experience greater decreases in in FEV_1 and more severe airway obstruction over time compared with those with fewer exacerbations.[20-23] Given the mean treatment duration (approximately 3.5 years)

and age of these patients, a decrease in lung function over time might be part of the natural progression of disease in this population. Alternatively, this decrease might have been related to a decrease in other maintenance therapies, such as inhaled corticosteroids and long-acting β_2-agonists, which might have been reduced over the study period or related to risk from their underlying asthma. A possible explanation for this gradual decrease in lung function, even when exacerbations and eosinophil counts remain controlled, is that FEV_1 might not be directly associated with improvements in eosinophilic airway inflammation; this implies that in patients with severe asthma, there is a dissociation between lung function and risk of exacerbations.[24-26]

Other biologic therapies approved for use in patients with severe asthma include benralizumab, reslizumab, and omalizumab.[27-29] Benralizumab targets the IL-5 receptor α, which is expressed on eosinophils and basophils and induces apoptosis through antibody-dependent cell-mediated cytotoxicity.[30,31] Benralizumab has been reported to reduce asthma exacerbations with a favorable safety profile, despite a higher immunogenicity response in phase III trials[32,33] in comparison with the mepolizumab phase III trials. However, the long-term safety of benralizumab is uncertain because treatment results in the near-complete depletion of eosinophils,[31,34] which can result in a loss of regulatory immune functions after long-term exposure.[4,35] In contrast, during clinical trials, mepolizumab did not fully deplete blood eosinophil counts but consistently reduced them to approximately 40 cells/μL.[4]

Reslizumab is an anti–IL-5 mAb for intravenous administration that has also been shown to reduce exacerbations in patients with SEA.[36] In a recent open-label extension study (<24 months), reslizumab had a similar AE profile to that reported for mepolizumab, with worsening of asthma, upper respiratory tract infections, and headache being among the most commonly reported AEs.[37] Longer-term safety data for benralizumab and reslizumab are still lacking.

The EXCELS (A Study of Xolair to Evaluate Effectiveness and Long-Term Safety in Patients With Moderate to Severe Asthma, NCT00252135) study assessed the long-term safety of omalizumab (anti-IgE antibody) in patients with allergic asthma treated up to 5 years.[38] Results demonstrated a small increased risk of cardiovascular/cerebrovascular events in patients treated with omalizumab compared with patients not treated with omalizumab. The authors highlight that differences in asthma severity between cohorts might have contributed to this increased risk. No risk related to malignancies was identified.[38,39] Overall, current available data support a favorable risk/benefit ratio after long-term treatment with omalizumab and mepolizumab.

An intrinsic limitation on any long-term open-label study in a population with severe disease is the lack of a placebo-controlled arm from which to make robust clinical interpretations regarding any treatment-related outcomes. Considering that patients were more likely to experience an AE in this study compared with a shorter study, exposure-adjusted rates were calculated to account for the increased length of exposure to mepolizumab. Additionally, because of the attrition of patients at different intervals at the end of the observational period, some efficacy end points should be interpreted with caution because results from the latter stages of the trial are based on fewer patients compared with the first 2 to 3 years.

There are limitations on the generalizability of results from open-label extension studies to clinical practice because of the inclusion/exclusion criteria and lower frequency of comorbidities among the study population. Patients in this study were selected from the DREAM study population, and as fully described in the Methods section, those considered to be at increased risk of potentially mepolizumab-related AEs or SAEs were excluded, which could have introduced selection bias. Finally, the dose of other controller medications was not regulated throughout the study period. As such, it is difficult to establish comparisons with controlled clinical trials in which controller medication use is regulated; however, this lack of controller use regulation should be considered to reflect the real-world clinical experience of patients receiving long-term mepolizumab treatment.

In conclusion, this study represents the longest clinical experience to date with an anti–IL-5 monoclonal therapy in patients with severe asthma. The results of this long-term open-label extension with mepolizumab exposure for up to 4.5 years in patients with SEA add to the overall safety profile of mepolizumab in this patient population. This study additionally demonstrates the durability of clinical and pharmacodynamic responses after long-term mepolizumab treatment, with improvements consistent with those reported in previous randomized clinical trials and maintained for up to 4.5 years. Overall, these results support the use of mepolizumab as a long-term treatment choice for patients with SEA.

Clinical implications: After long-term use in patients with SEA, mepolizumab maintains clinical effectiveness and continues to demonstrate a favorable safety profile, with no evidence of inducing neutralizing antibodies.

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METHODS

Further exclusion criteria

Patients were excluded from participation in the COLUMBA study if they had any of the following: severe or clinically significant cardiovascular disease uncontrolled with standard treatment, increased liver function test results, any current malignancy or previous history of cancer in remission for less than 12 months before screening, a positive hepatitis B surface antigen screen at visit 1, or a parasitic infection within 6 months of visit 2. Pregnant women, current smokers, and patients who received omalizumab treatment within the past 130 days were also excluded.

Protocol-defined stopping criteria

Each of the following constituted a protocol-defined stopping criterion: the safety profile for the patient was no longer positive in the opinion of the investigator, the patient was withdrawn by their physician, the patient withdrew consent, or mepolizumab became commercially available in the relevant participating country.

AESIs

Within the mepolizumab clinical development program, AESIs include systemic (allergic/hypersensitivity and nonallergic) reactions, local injection-site reactions, infections (including serious and opportunistic infections), malignancies, serious cardiac, vascular and thromboembolic events, and serious ischemic events.

Cardiovascular events adjudicated by a Clinical Endpoint Committee

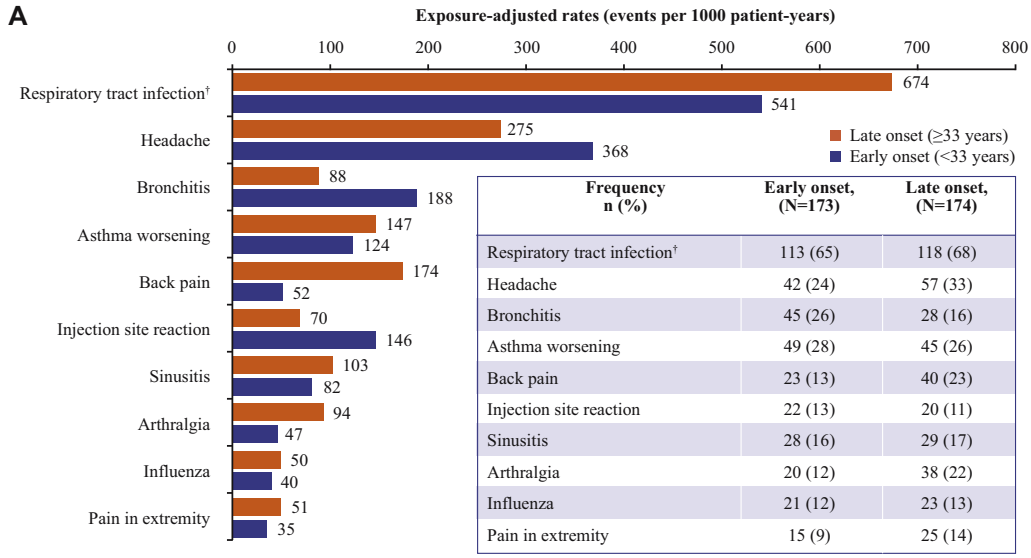
The following cardiovascular events were sent for adjudication by a Clinical Endpoint Committee: cerebrovascular events/stroke or transient ischemic attack, congestive heart failure, deep venous thrombosis, myocardial infarction/unstable angina, and peripheral arterial thrombosis embolism.

Definition of an exacerbation

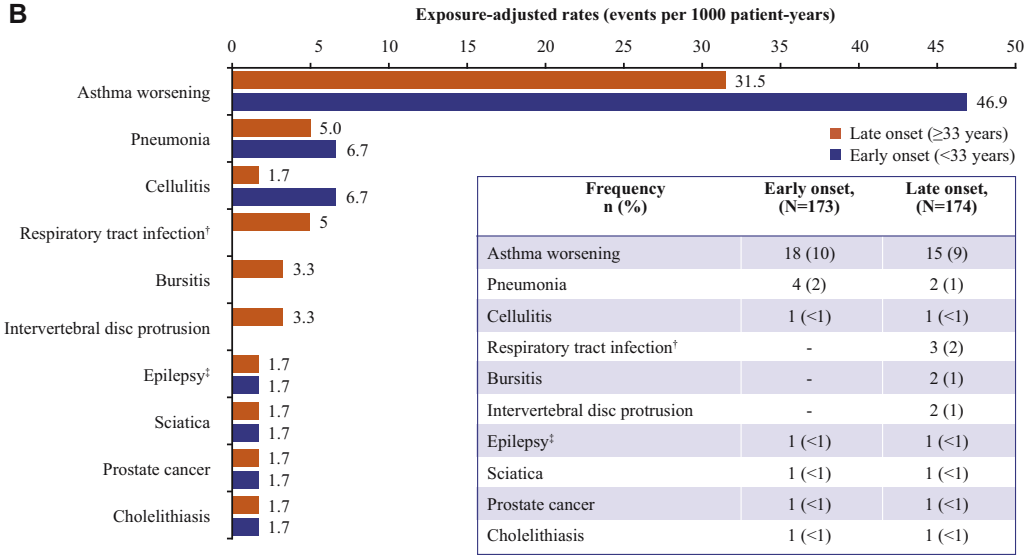
An exacerbation was defined as a worsening of asthma that required systemic corticosteroids, hospitalization, or an emergency department visit. Systemic corticosteroids comprised oral or intravenous corticosteroids for 3 or more days or a single intramuscular subcutaneous dose; for patients receiving maintenance systemic corticosteroids, at least double the existing maintenance dose was required for 3 or more days.

Participating countries

Argentina, Australia, Canada, Chile, France, Germany, Poland, Romania, the Russian Federation, South Korea, Ukraine, the United Kingdom, and the United States.



Frequency n (%)	Early onset, (N=173)	Late onset, (N=174)
Respiratory tract infection†	113 (65)	118 (68)
Headache	42 (24)	57 (33)
Bronchitis	45 (26)	28 (16)
Asthma worsening	49 (28)	45 (26)
Back pain	23 (13)	40 (23)
Injection site reaction	22 (13)	20 (11)
Sinusitis	28 (16)	29 (17)
Arthralgia	20 (12)	38 (22)
Influenza	21 (12)	23 (13)
Pain in extremity	15 (9)	25 (14)



Frequency n (%)	Early onset, (N=173)	Late onset, (N=174)
Asthma worsening	18 (10)	15 (9)
Pneumonia	4 (2)	2 (1)
Cellulitis	1 (<1)	1 (<1)
Respiratory tract infection†	-	3 (2)
Bursitis	-	2 (1)
Intervertebral disc protrusion	-	2 (1)
Epilepsy‡	1 (<1)	1 (<1)
Sciatica	1 (<1)	1 (<1)
Prostate cancer	1 (<1)	1 (<1)
Cholelithiasis	1 (<1)	1 (<1)

FIG E1. Summary of on-treatment AEs occurring in more than 10% of patients **(A)** and on-treatment SAEs occurring in more than 1 patient by age of asthma onset (as-treated population; **B**). *AEs were listed in line with Fig 3. -, AEs that were not reported in these populations. †Respiratory tract infection encompasses all AEs reported as (1) viral upper respiratory tract infection; (2) upper respiratory tract infection; (3) respiratory tract infection; (4) lower respiratory tract infection; (5) respiratory tract infection, viral; (6) lower respiratory tract infection, viral; and (7) upper respiratory tract infection, bacterial. ‡One patient with early-onset asthma had a childhood history of epilepsy.

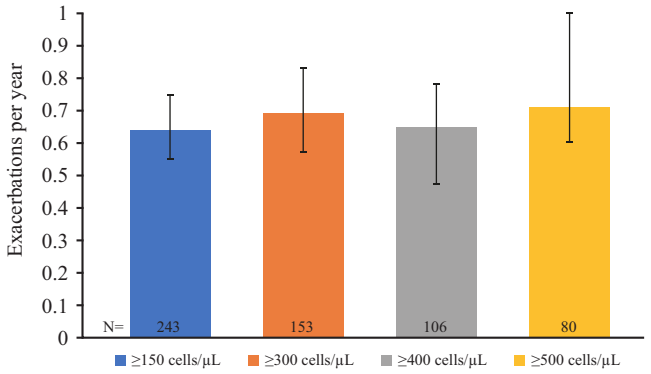


FIG E2. Annualized rate of on-treatment exacerbations by baseline blood eosinophil count.

TABLE E1. Summary of AEs leading to patient withdrawal from the trial or permanent discontinuation of study drug

AE leading to patient withdrawal	No. (%)
Any event	19 (5)
Asthma worsening	3 (<1)
Respiratory arrest	1 (<1)
Allergic rhinitis	1 (<1)
Sleep apnea syndrome	1 (<1)
Bundle branch block left	1 (<1)
Acute cardiac failure	1 (<1)
Myocardial infarction	1 (<1)
Stress myocardiopathy	1 (<1)
Injection-site reaction	1 (<1)
Peripheral edema	1 (<1)
Sudden death	1 (<1)
Breast cancer	1 (<1)
Breast cancer, stage I	1 (<1)
Prostate cancer	1 (<1)
Conjunctivitis	1 (<1)
Sinusitis	1 (<1)
Cerebral hemorrhage	1 (<1)
Dizziness	1 (<1)
Allergic conjunctivitis	1 (<1)
Hypersensitivity	1 (<1)
Alanine aminotransferase, increased level	1 (<1)
Aspartate aminotransferase, increased level	1 (<1)
Gamma-glutamyltransferase, increased level	1 (<1)
Obesity	1 (<1)
Atopic dermatitis	1 (<1)

More than 1 AE leading to withdrawal/discontinuation could be listed per patient.

TABLE E2. Summary of on-treatment AEs* occurring in more than 10% of patients and on-treatment SAEs occurring in more than 1 patient by age of asthma onset (as-treated population)

	Early onset, age <33 y (n = 173)	Late onset, age ≥33 y (n = 174)
On-treatment AEs, no. (%)		
Any AE	162 (94%)	164 (94%)
Respiratory tract infection†	113 (65%)	118 (68%)
Asthma worsening	49 (28%)	45 (26%)
Bronchitis	45 (26%)	28 (16%)
Headache	42 (24%)	57 (33%)
Sinusitis	28 (16%)	29 (17%)
Back pain	23 (13%)	40 (23%)
Injection-site reaction	22 (13%)	20 (11%)
Influenza	21 (12%)	23 (13%)
Arthralgia	20 (12%)	38 (22%)
Pain in extremity	15 (9%)	25 (14%)
On-treatment SAEs, no. (%)		
Any SAE	42 (24%)	37 (21%)
Asthma worsening	18 (10%)	15 (9%)
Pneumonia	4 (2%)	2 (1%)
Cellulitis	1 (<1%)	1 (<1%)
Respiratory tract infection†	-	3 (2%)
Bursitis	-	2 (1%)
Intravertebral disc protrusion	-	2 (1%)
Epilepsy‡	1 (<1%)	1 (<1%)
Sciatica	1 (<1%)	1 (<1%)
Prostate cancer	1 (<1%)	1 (<1%)
Cholelithiasis	1 (<1%)	1 (<1%)

Data are presented as numbers (percentage).
-, AEs that were not reported in these populations.
*AEs were listed in line with Fig 3.
†Respiratory tract infection encompasses all AEs reported as (1) viral upper respiratory tract infection; (2) upper respiratory tract infection; (3) respiratory tract infectionl (4) lower respiratory tract infection; (5) respiratory tract infection, viral; (6) lower respiratory tract infection, viral; and (7) upper respiratory tract infection, bacterial.
‡One patient with early-onset asthma had a childhood history of epilepsy.

TABLE E3. Summary of the on-treatment AEs occurring in more than 10% of patients and on-treatment SAEs occurring in more than 1 patient by the presence of rhinosinusitis at screening* (as-treated population)

	Patients with chronic rhinosinusitis at screening (n = 41)	Patients without chronic rhinosinusitis at screening (n = 306)
On-treatment AEs, no. (%)		
Respiratory tract infection†	32 (78%)	199 (65%)
Asthma worsening	13 (32%)	81 (26%)
Bronchitis	8 (20%)	65 (21%)
Headache	14 (34%)	85 (28%)
Sinusitis	19 (46%)	38 (12%)
Back pain	8 (20%)	55 (18%)
Injection-site reaction	8 (20%)	34 (11%)
Influenza	7 (17%)	37 (12%)
Arthralgia	10 (24%)	48 (16%)
Pain in extremity	3 (7%)	37 (12%)
On-treatment SAEs, no. (%)		
Asthma worsening	3 (7%)	30 (10%)
Pneumonia	1 (2%)	5 (2%)
Cellulitis	-	2 (<1%)
Respiratory tract infection†	-	3 (<1%)
Bursitis	1 (2%)	1 (<1%)
Intravertebral disc protrusion	-	2 (<1%)
Epilepsy‡	1 (2%)	1 (<1%)
Sciatica	-	2 (<1%)
Prostate cancer	1 (2%)	1 (<1%)
Cholelithiasis	1 (2%)	1 (<1%)

Data are presented as number (percentage).
-, AEs that were not reported in these populations.
*AEs were listed in line with Fig 3.
†Respiratory tract infection encompasses all AEs reported as (1) viral upper respiratory tract infection; (2) upper respiratory tract infection; (3) respiratory tract infection; (4) lower respiratory tract infection; (5) respiratory tract infection, viral; (6) lower respiratory tract infection, viral; and (7) upper respiratory tract infection, bacterial.
‡One patient without chronic rhinosinusitis had a childhood history of epilepsy.

TABLE E4. Overview of exacerbation rate per year across the DREAM and COLUMBA studies

	Exacerbation rate/year		
Treatment period	**Placebo (n = 77)**	**Mepolizumab (n = 270)**	**Total (n = 347)**
Subjects with ≥52 weeks of open-label data	n = 69	n = 254	n = 323
Pretreatment*			3.47
On treatment during DREAM†	2.03	1.17	1.35
Off treatment between DREAM and COLUMBA‡			1.79
On treatment during COLUMBA§			
Week 0–52§			0.80
Subjects with ≥104 weeks of open-label data	n = 62	n = 240	n = 302
Pretreatment*			3.48
On treatment during DREAM†	2.18	1.13	1.35
Off treatment between DREAM and COLUMBA‡			1.66
On treatment during COLUMBA§			
Week 0–52			0.74
Week >52–Week 104			0.82
Subjects with ≥156 weeks of open-label data	n = 62	n = 224	n = 286
Pretreatment*			3.49
On treatment during DREAM†	2.18	1.07	1.31
Off treatment between DREAM and COLUMBA‡			1.67
On treatment during COLUMBA§			
Week 0–52			0.71
Week >52–Week 104			0.82
Week >104–Week 156			0.71
Subjects with ≥208 weeks of open-label data	n = 39	n = 131	n = 170
Pretreatment*			3.17
On treatment during DREAM†	2.18	1.06	1.32
Off treatment between DREAM and COLUMBA‡			1.62
On treatment during COLUMBA§			
Week 0–52			0.79
Week >52–Week 104			0.90
Week >104–Week 156			0.70
Week >156–Week 208			0.80

*Twelve months before enrollment in the DREAM study.

†Weeks 0 to 52, double-blind phase of the DREAM study. Treatment included intravenously administered doses of mepolizumab (75, 250, and 750 mg) or placebo.

‡Subjects were being treated with standard of care by investigators during this period.

§All subjects received open-label 100 mg of mepolizumab administered subcutaneously during the COLUMBA study in addition to standard of care.