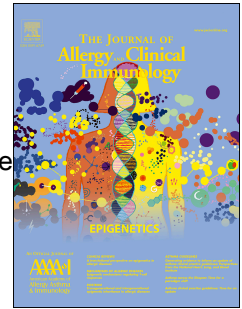


Accepted Manuscript

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

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PII: S0091-6749(18)31479-9

DOI: <https://doi.org/10.1016/j.jaci.2018.09.033>

Reference: YMAI 13678

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 10 July 2018

Revised Date: 7 September 2018

Accepted Date: 20 September 2018

Please cite this article as: Khatri S, Moore W, Gibson PG, Leigh R, Bourdin A, Maspero J, Barros M, Buhl R, Howarth P, Albers FC, Bradford ES, Gilson M, Price RG, Yancey SW, Ortega H, Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma, *Journal of Allergy and Clinical Immunology* (2018), doi: <https://doi.org/10.1016/j.jaci.2018.09.033>.

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COLUMBA: Long-term safety and durability of mepolizumab response in patients with severe eosinophilic asthma

Study design and treatment

Open
label

Single
arm

Multi-
center

Extension
study



Mepolizumab
100 mg SC
every 4 weeks

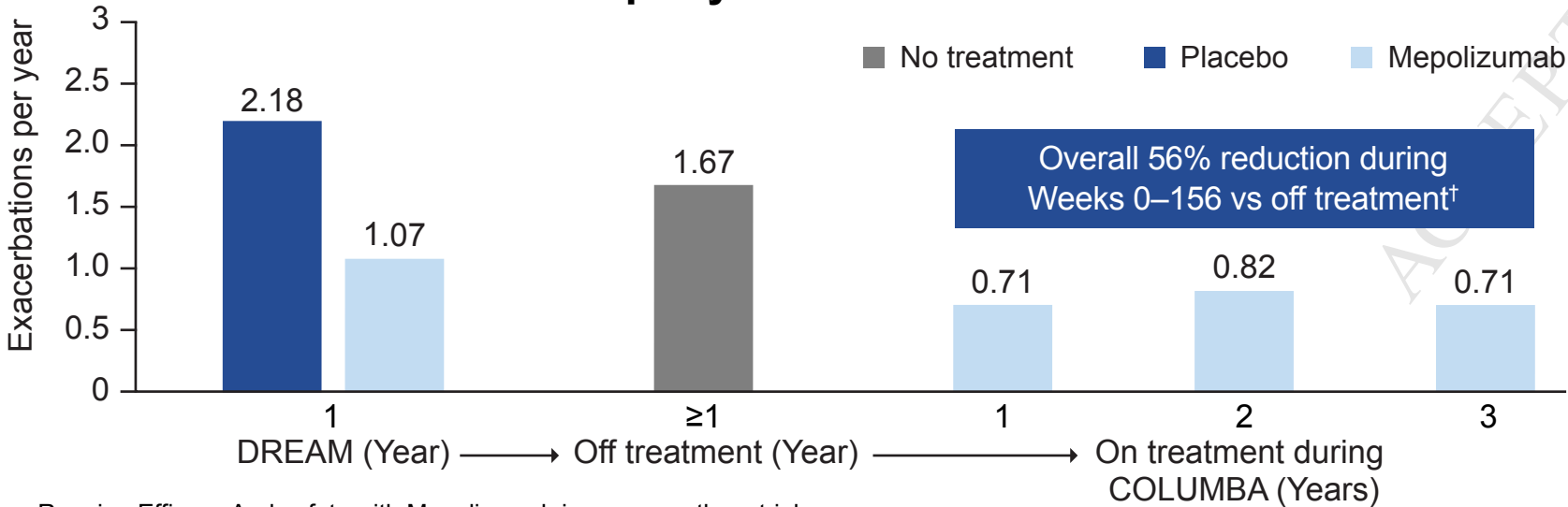


Patients treated
for up to
4.5 years



347 patients
treated

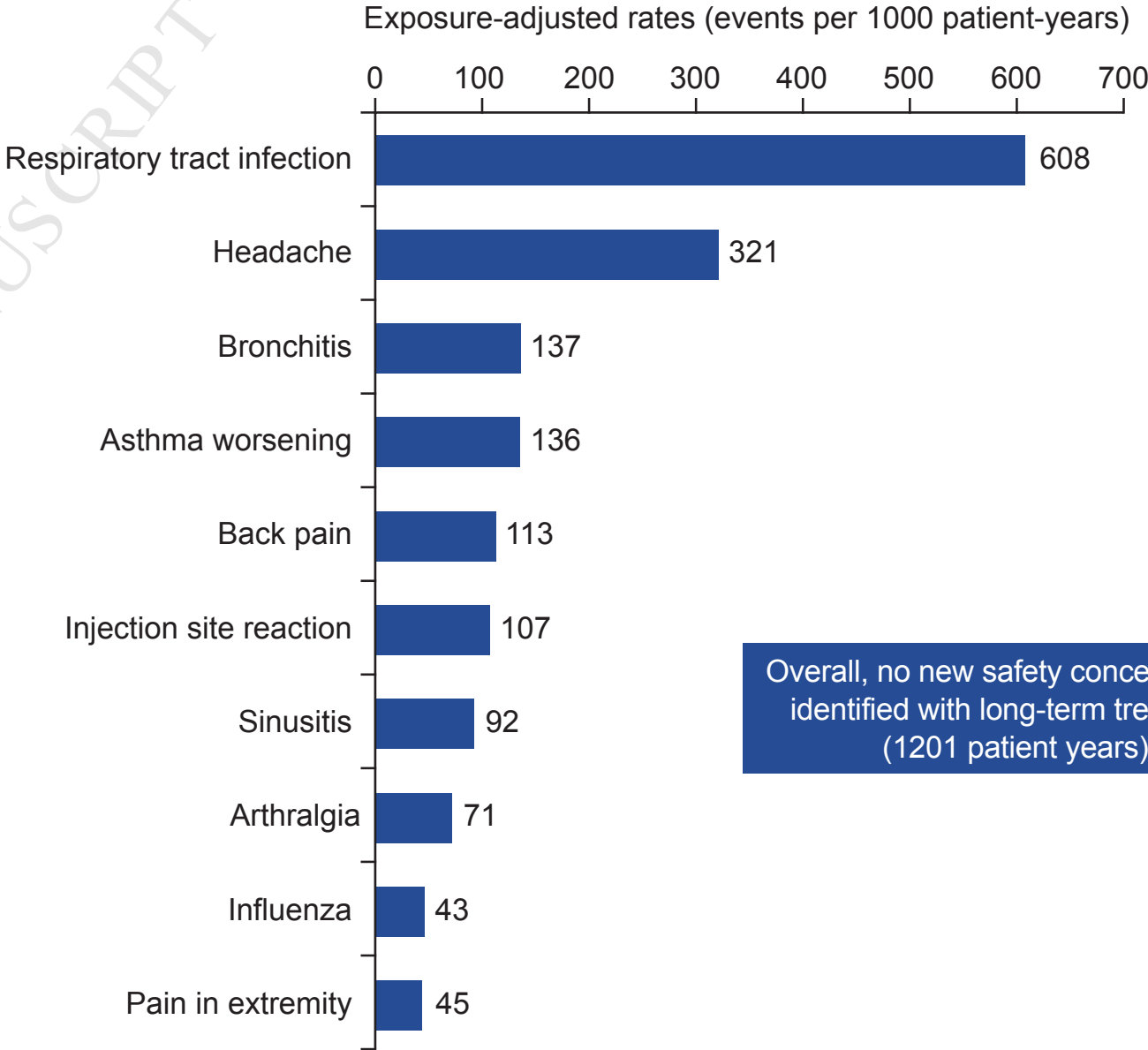
Exacerbation rates per year across DREAM* and COLUMBA†



*Dose Ranging Efficacy And safety with Mepolizumab in severe asthma trial

†Based on 286 patients with ≥156 weeks of open-label data in COLUMBA

On-treatment AEs occurring in >10% of patients during COLUMBA



Overall, no new safety concerns were
identified with long-term treatment
(1201 patient years)

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

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Authors' contributions: SY and HO were involved in the conception and design of the study. SK, WM, PGG, RL, AB, JM, MB, PH and RB were involved in the acquisition of data. All authors were involved in the analysis and interpretation of the data, development of the manuscript and provided final approval of the version to be published.

Funding sources and role: This study was funded by GlaxoSmithKline (GSK ID: MEA115666 ClinicalTrials.gov number: NCT01691859).

Data sharing statement

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

Abstract

Background: Mepolizumab has demonstrated favorable safety and efficacy profiles in placebo-controlled trials ≤ 12 months' duration; however, long-term data are lacking.

Objective: To evaluate the long-term safety and efficacy of mepolizumab in patients with severe eosinophilic asthma (SEA).

Methods: COLUMBA (NCT01691859) was an open-label extension study in patients with SEA previously enrolled in DREAM (NCT01000506). Patients received 100mg subcutaneous mepolizumab every 4 weeks plus standard of care, until a protocol-defined stopping criterion was met. Safety endpoints included frequency of adverse events (AEs), serious AEs (SAEs), and AEs of special interest. Efficacy endpoints included annualized exacerbation rate, changes from baseline in Asthma Control Questionnaire (ACQ)-5 score, and blood eosinophil counts. Immunogenicity was also assessed.

Results: Overall, 347 patients were enrolled for an average of 3.5yrs (maximum: 4.5yrs; 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 on-treatment SAE; there were 6 deaths, none assessed as related to mepolizumab. For patients with ≥ 156 weeks enrollment, the exacerbation rate was 0.74 events/year (Weeks 0–156), a 56% reduction from the off-treatment period between DREAM and COLUMBA. For all patients, at the first post-baseline assessment, the mean ACQ-5 score was reduced by 0.47 points and blood eosinophil counts 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.

Clinical Implications: Following long-term use in patients with severe eosinophilic asthma, mepolizumab maintains clinical effectiveness and continues to demonstrate a favorable safety profile, with no evidence of inducing neutralizing antibodies.

Capsule Summary: This long-term extension study of mepolizumab in patients with severe eosinophilic asthma (exposure ≤ 4.5 years) identified no new safety concerns. Safety, immunogenicity, and efficacy profiles were durable and similar to previous, placebo-controlled clinical trials.

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

Abbreviations

ACQ-5, Asthma Control Questionnaire 5

ADA, anti-drug antibodies

AE, adverse event

AESI, adverse event of special interest

AT, as treated

CI, confidence intervals

ECG, electrocardiogram

ED, emergency department

FEV₁, forced expiratory volume in 1 second

FVC, forced vital capacity

ICS, inhaled corticosteroid

IL-5, interleukin-5

IV, intravenous

LABA, long-acting β_2 -agonists

LAMA, long-acting muscarinic antagonist

LTRA, long-acting leukotriene receptor antagonist

MCID, minimal clinically important difference

NAb, neutralizing drug antibody

OCS, oral corticosteroids

SABA, short-acting β_2 -agonists

SAE, serious adverse event

SC, subcutaneous

SD, standard deviation

SEA, severe eosinophilic asthma

SEER, Surveillance Epidemiology and End Results

Introduction

Severe asthma is a heterogeneous condition in which patients present with different clinical and physiological 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 treatment response.

Mepolizumab, an anti-interleukin-5 (IL-5) humanized monoclonal antibody, 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 four randomized placebo-controlled trials: DREAM (NCT01000506),(5) MENSA (NCT01691521),(6) SIRIUS (NCT01691508),(7) and, MUSCA (NCT02281318).(8) In comparison to 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 $\geq 50\%$ 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)

Further to 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 (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 to 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 (GSK ID MEA115666; NCT01691859) (10) was a multicenter, open-label, long-term safety study conducted in patients who had previously participated in the DREAM study (GSK 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 (IV) mepolizumab, 75 mg, 250 mg, 750 mg, or placebo, every 4 weeks for 52 weeks. Patients were invited to participate in COLUMBA 12–28 months after they completed the DREAM study. This study was conducted in accordance with ICH Good Clinical Practice, applicable country specific requirements and ethical principles outlined in the Declaration of Helsinki. All patients provided written informed consent prior to any study-related activities.

Patients

To be eligible for inclusion in COLUMBA, patients had to have been randomized and received at least two doses of treatment (mepolizumab or placebo) in the DREAM study,⁽⁵⁾ and to have been receiving an asthma controller medication for ≥ 12 weeks prior to 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, which 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 Supplementary Material.

Treatments

During COLUMBA, all patients received mepolizumab 100 mg subcutaneously (SC) every 4 weeks, regardless of previous treatment regimen, until a protocol-defined stopping criterion was met (Supplementary Materials). Patients continued to receive standard of care asthma therapy for the duration of the study, which could be adjusted at the discretion of their physician.

Endpoints

Safety Endpoints

The primary safety endpoint was the frequency all AEs, SAEs, and AEs of special interest (AESIs). All AESIs are listed within the Supplementary Materials. AEs were recorded on a worksheet by patients and documented by study staff at each visit. Deaths from any cause and selected cardiovascular events (Supplementary Materials) were adjudicated by a Clinical Endpoint Committee.

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

Efficacy Endpoints

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 Supplementary Materials. 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 forced expiratory volume in 1 second (FEV₁), was conducted at baseline and every 12–24 weeks throughout the study. Patients were asked to withhold short-acting β_2 -agonists (SABAs) for ≥ 6 hours and long-acting β_2 -agonists (LABAs) for ≥ 12 hours prior to the clinic visit, if possible. Blood eosinophil counts were assessed at baseline and at specified times throughout the study.

Immunogenicity Endpoints

Immunogenicity testing for the presence of anti-drug antibodies (ADAs), defined as any antibody isotype directed against mepolizumab, was performed in blood by 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 using the as treated (AT) population, defined as all patients who received at least one dose of open-label mepolizumab. All endpoints were summarized using appropriate descriptive statistics (mean/geometric mean, median, standard deviation [SD], range).

AEs were summarized 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 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% confidence intervals (CI) were calculated. Asthma control and spirometry endpoints 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 non-zero result) was imputed prior to log-transformation. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Post hoc subgroup analyses were conducted to assess the annualized on-treatment exacerbation rate by baseline blood eosinophil count using the subgroups: ≥ 150 cells/ μL , ≥ 300 cells/ μL , ≥ 400 cells/ μL , and ≥ 500 cells/ μL . Additionally AEs, SAEs, exacerbation rate and ACQ-5 score were assessed post hoc in patients with early (< 33 years of age) and late (≥ 33 years of age) onset 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 (Supplementary Materials). Overall, 362 patients were enrolled in the study, and 347 were included in the AT population, corresponding to 56% of the DREAM intent-to-treat population. An overview of patient flow through the study is shown in **Figure 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 due to an AE; the only AE resulting in >1 patient withdrawal was asthma worsening (n=3, <1%) (Supplementary Table 1). A summary of time to study discontinuation is presented in **Figure 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 1**. 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 four treatment arms of the DREAM study (22%–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.

Safety endpoints

Overall, 326 (94%) patients experienced at least one on-treatment AE, giving 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 (**Figure 3A**). 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 $\geq 3\%$ were injection site reaction (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 2**). On-treatment SAEs reported in >1 patient are summarized in **Figure 3B**. Six fatalities were reported: one patient experienced sudden death; one patient died of respiratory arrest; one patient died of morbid obesity, chronic asthma

and sleep apnea; one patient died of myocardial infarction; one patient died of acute heart failure; and one 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/ μ L and a history of sinusitis, which was resolved prior to entry into DREAM. This death was not adjudicated as the information for adjudication was not available. No fatal SAEs were assessed as possibly related to the study treatment.

A post hoc analysis of adverse events 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 extremity were more frequently reported in the late onset group (those diagnosed ≥ 33 years, $n=174$) compared with the early onset group (those diagnosed <33 years, $n=173$; Supplementary Table 2). In addition, the frequency of reported bronchitis was higher in the early onset group compared with the late onset group. Overall, the proportion of patients reporting SAEs was similar between the two groups (Supplementary Figure 1).

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%) (Supplementary Table 3).

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

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

Efficacy Endpoints

Over the study period, the annualized rate of on-treatment exacerbations across all enrolled patients was 0.68 events/year (95% CI: 0.60, 0.78), representing a 61% reduction from the off-treatment period between DREAM and COLUMBA (1.74 events/year). For patients with ≥ 156 weeks enrollment in COLUMBA, the mean annualized rate of exacerbations was 0.74 events/year for Weeks 0–156, representing a 79% reduction from the 12 months prior to DREAM, and a 56% reduction from the off-treatment period between DREAM and COLUMBA (**Figure 4A**, **Supplementary Table 4**). Post hoc analysis showed similar rates of on-treatment exacerbations for all baseline blood eosinophil count subgroups (Supplementary Figure 2). In addition, similar annualized rates of on-treatment exacerbations were observed when patients were grouped by early (<33 years; 0.69 events/year [95% CI: 0.58, 0.83]) or late (≥ 33 years; 0.67 events/year [95% CI: 0.55, 0.82]) asthma onset. Consistent with the previously discussed sub-group 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/year).

Improvements in asthma control were observed at the first post-baseline 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 points at each post-baseline assessment (**Figure 4B**). In addition, similar improvements in ACQ-5 scores were seen in patients who were diagnosed with early (<33 years of age) or late (≥ 33 years of age) onset asthma. Mean reductions in ACQ-5 score ranged from 0.58 points (Week 124) to 0.07 points (Week 228) in the early onset group and 0.75 (Week 124) to 0.45 (Week 188) in the late onset group.

Pre-bronchodilator FEV₁ values initially increased from baseline (mean [SD]: 1811 mL [696.2]; percent predicted mean [SD]: 60.1 [18.9]) to a mean (SD) of 1955 mL (728) at Week 24 (percent predicted mean [SD]: 65.0 [19.8]) and gradually declined over the remainder of the study period. At Week 200, the mean pre-bronchodilator FEV₁ showed no clinically significant difference from baseline (1855 mL [660]; percent predicted: 61.5 [17.1]; **Figure 4C**). Blood eosinophil counts were

suppressed by 78% from a geometric mean (SD logs) of 240 cells/ μ L (1.016) at baseline to 50 cells/ μ L (0.951) at Week 4 and remained suppressed throughout the study period (**Figure 4D**).

Immunogenicity Endpoints

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

At any time post-baseline, 27/346 (8%) patients tested positive for ADAs. Titer values post-baseline were low for all positive patients (≤ 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 an anti-IL-5 biologic, mepolizumab, in patients with SEA. The observed safety and immunogenicity profile of long-term, mepolizumab SC treatment was similar to that seen in previous randomized, placebo-controlled trials of mepolizumab with IV and SC administration, and the COSMOS 52-week extension study.(5-8, 12). 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 following long-term exposure. As reported previously,(13) cessation of mepolizumab at the end of DREAM led to a general decline 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 impact 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, where 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) The exposure-adjusted rates of headaches 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 COSMOS and COLUMBA, respectively.

Six deaths were reported during the study following 1201 patient-years exposure to mepolizumab, all of which were considered unrelated to mepolizumab treatment by the investigator. This rate is

similar to rates in treatment and placebo arms of the original mepolizumab asthma registration studies,(5-7) in which three deaths were reported following 687 patient-years exposure to mepolizumab and two deaths were reported following 284 patient-years exposure to placebo. Finally, the number of cancers observed in the study population was similar to age- and gender-adjusted incidence rates from the Surveillance Epidemiology and End Results (SEER) Registry in the United States.(14) Incidence rates of prostate and breast cancers in this study were 1.7 and 0.83 events per 1000 patient-years, respectively, compared to 1.5 and 0.67 events per patient-years in the SEER Registry for 2007–2011.(15, 16)

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 IV mepolizumab in DREAM 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 following 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 (MCID) of 0.5 points at each post-baseline assessment.(17) 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.(17) As such, a clinically meaningful difference in asthma control may be experienced even if the reduction in ACQ-5 score reported is less than 0.5 points. While in the overall population we observed consistent durability of clinical response, some patients may not respond fully or maintain

the same level of response over time. There is limited data to clearly understand the mechanisms implicated in a potential loss of efficacy among biologics in the respiratory space. One report (18) indicates that we need to carefully characterize these patients in terms of comorbid conditions, environmental triggers, and non-type 2 inflammation, and also ensure 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 declined to approximately baseline values at Week 200, demonstrating a stabilization of the impact 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 decline in FEV₁ and more severe airway obstruction over time compared with those with fewer exacerbations.(19-22) Given the mean treatment duration (~3.5 years) and age of these patients, a decline in lung function over time may be part of the natural progression of disease in this population. Alternatively, this decline may have been related to a decrease in other maintenance therapies, such as inhaled corticosteroid (ICS) and LABAs, which may have been reduced over the study period, or related to risk from their underlying asthma. A possible explanation for this gradual decline in lung function even when exacerbations and eosinophil counts remain controlled, is that FEV₁ may 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.(23-25)

Other biologic therapies approved for use in severe asthma include benralizumab, reslizumab, and omalizumab.(26-28) Benralizumab targets the IL-5 receptor α expressed on eosinophils and basophils, and induces apoptosis through antibody-dependent cell-mediated cytotoxicity.(29, 30) Benralizumab has been reported to reduce asthma exacerbations with a favorable safety profile, despite a higher immunogenicity response in Phase III trials(31, 32) in comparison to the mepolizumab phase III trials. However, the long-term safety of benralizumab is uncertain, as treatment results in the near-complete depletion of eosinophils,(30, 33) which may result in a loss of regulatory immune functions following long-term exposure.(4, 34) In contrast, during clinical trials mepolizumab did not fully deplete blood eosinophil counts, but consistently reduced them to approximately 40 cells/ μ L.(4) Reslizumab is an anti-IL-5 monoclonal antibody for IV administration that has also been shown to reduce exacerbations in patients with SEA.(35) 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.(36) Longer-term safety data for benralizumab and reslizumab are still lacking. The EXCELS study assessed the long-term safety of omalizumab (anti-immunoglobulin E antibody) in patients with allergic asthma treated up to 5 years.(37) 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 may have contributed to this increased risk. No risk related to malignancies was identified.(37, 38) 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, due to the attrition of patients at different intervals at the end of the observational period, some efficacy endpoints should be interpreted with caution as results from the latter stages of the trial are based on fewer patients compared with the first 2–3 years.

There are limitations on the generalizability of results from open-label extension studies to clinical practice due to the inclusion/exclusion criteria and lower frequency of comorbidities amongst 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.

Conclusion

This study represents the longest clinical experience to date with an anti-IL-5 monoclonal therapy in 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 following 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.

Acknowledgments

This study was funded by GlaxoSmithKline (GSK ID MEA115666; NCT01691859).

SY and HO contributed to the conception and design of the study. SK, WM, PGG, RL, AB, JM, MB, RB, and PH contributed to the acquisition of the data. All authors contributed to the analysis and interpretation of the data, development of the manuscript and provided final approval of the version to be published.

Editorial support (in the form of writing assistance, including development of the initial draft based on author feedback, assembling tables and figures, collating authors comments, grammatical editing, and referencing) was provided by Natasha Dean, MSc, and Susan Parker, PhD, at Fishawack Indicia Ltd, UK, and was funded by GSK.

Conflicts of interest

SK reports being an investigator in clinical trials in relation to GSK and Boston Scientific, for which her institution is compensated for time related to the study. WM reports receiving research grants from GSK, AZ, Boehringer Ingelheim, Novartis, Pearl Therapeutics, Sanofi Regeneron, and NIH/NHLBI, and has been an advisory board consultant for AZ and Sanofi Regeneron. PGG reports receiving personal fees from AstraZeneca, GSK and Novartis, and a research grant from GSK and NHMRC. RL reports receiving honoraria and speakers' fees from AstraZeneca, Boehringer Ingelheim, GSK, Novartis, and TEVA. His institution has also received research funding from AstraZeneca, GSK, MedImmune, Novartis, and Sanofi for clinical trials in which he was a site investigator. AB reports receiving personal fees, research grants and non-financial support from GSK; personal fees and non-financial support from AstraZeneca and Novartis; research grants from MSD; research grant and personal fees from Actelion; and, personal fees and non-financial support from Chiesi. JM reports attending focus groups and boards for AstraZeneca and receiving personal fees from Novartis, AstraZeneca, GSK, Sanofi and Uriach. MB reports receiving honoraria from Boehringer Ingelheim and Grifols for lectures and Advisory boards, and has been involved as Principal Investigator in clinical trials for GSK, Pearl therapeutics, Sanofi Aventis, and Chiesi. RB reports personal fees from AstraZeneca, Chiesi, Teva, and Cipla, grants and personal fees from Boehringer Ingelheim, Novartis and Roche, and grants from GlaxoSmithKline, all of which are outside the submitted work. FCA, EB, MG, RGP, PH, and SY, are all employees of GlaxoSmithKline and hold stocks/shares in GSK. HO is a

former employee of GSK and holds stocks/shares in GSK.

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Table 1. Baseline demographic and clinical characteristics (as-treated population)

Characteristic	Mepolizumab 100 mg SC (N=347)
Age, year, mean (SD)	52.2 (10.73)
Gender, female, n (%)	224 (65)
Race, n (%)	
White	318 (92)
Asian	18 (5)
Other	11 (3)
Non-Hispanic, n (%)	306 (88)
Body mass index, kg/m ² , mean (SD)	28.6 (6.10)
Comorbidities of interest	
Allergic rhinitis or hay fever, n (%)	165 (48)
Chronic rhinosinusitis	41 (12)
Nasal polyposis	24 (7)
Duration of disease, years, mean (SD)	21.4 (14.22)
Age of onset of disease, years, median (range)	33 (0–66)
Lung function tests at baseline	
Pre-bronchodilator FEV1, mL, mean (SD)	1811 (696.2)
Pre-bronchodilator % predicted normal FEV1, mean (SD)	60.1 (18.89)
Pre-bronchodilator 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 (min, max)	270 (0, 1600)
Concurrent therapy, n (%)	
ICS [†]	347 (100)
LABA [‡]	339 (98)
SABA	315 (91)
Xanthine	75 (22)
LTRA	63 (18)
LAMA	51 (15)
Maintenance OCS use at baseline, n (%)	90 (26)
Period since completion of DREAM, months, median (range)	17.8 (12, 28)
Exacerbations since completion of DREAM	
Exacerbations, mean (SD)	2.7 (4.74)
Number of patients to experience ≥1 event (%)	280 (81)
Exacerbations requiring ED/hospitalization, mean (SD)	0.4 (0.83)
Number of patients to experience ≥1 event (%)	75 (22)
Exacerbations requiring hospitalization, mean (SD)	0.2 (0.59)
Number 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)

*Scale scores: 0=no impairment, 6=maximum impairment; [†]during DREAM, patients required ≥ 880 μg fluticasone propionate per day, however ICS doses may have been reduced following completion of DREAM; [‡]LABA was provided concomitant with ICS, as per standard of treatment guidelines. ACQ-5, Asthma Control Questionnaire-5; ED, emergency department; FEV₁, forced expiratory volume in 1 second; 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; SD, standard deviation

Table 2. 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)
AEs of Special Interest	
Systemic reactions	9 (3)
Allergic/hypersensitivity reactions*	8 (2)
Non-allergic 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 n (%).

*More than one 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 (39);

**cardiac disorders includes all events in Cardiac disorders System Organ Class; ^{††}identified through MedDRA SMQs.

AE, adverse event; MedDRA, medical dictionary for regulatory activities; SAE, serious adverse event; SC, subcutaneous; SMQs, standardized MedDRA queries

Figure legends

Figure 1. Patient flow through COLUMBA

*Following completion of COLUMBA, patients could enter a further mepolizumab study (201810 or 201956) or choose to receive mepolizumab commercially outside of a clinical trial.
AT, as treated; IV, intravenous; ITT, intent-to-treat; SC, subcutaneous.

Figure 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

Figure 3. Summary of (A) on-treatment AEs occurring in >10% of patients and (B) on-treatment SAEs occurring in >1 patient (as-treated population)

*Respiratory tract infection encompasses all adverse events 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.
AE, adverse event; SAE, serious adverse event.

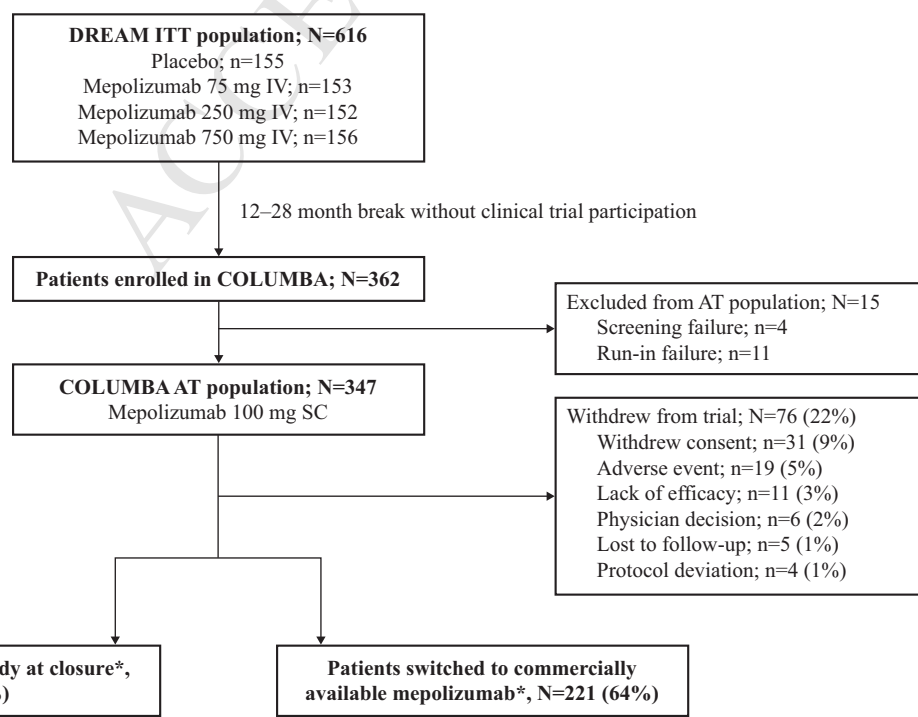
Figure 4. Summary of efficacy endpoints: (A) exacerbation rate per year across DREAM and COLUMBA*; (B) ACQ-5 score change from baseline; (C) pre-bronchodilator FEV₁ change from baseline; (D) blood eosinophil geometric mean ratio to baseline

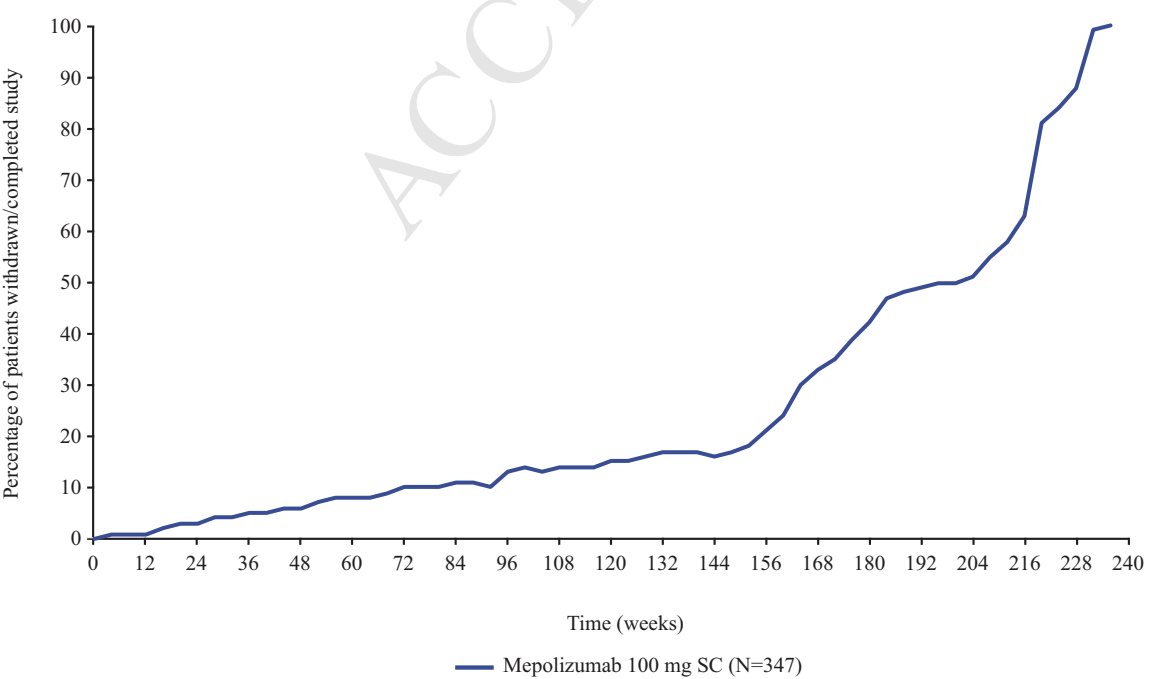
*A total of 286 patients with ≥156 weeks of open-label data in COLUMBA are summarized (DREAM: placebo [n=62], mepolizumab [n=224])

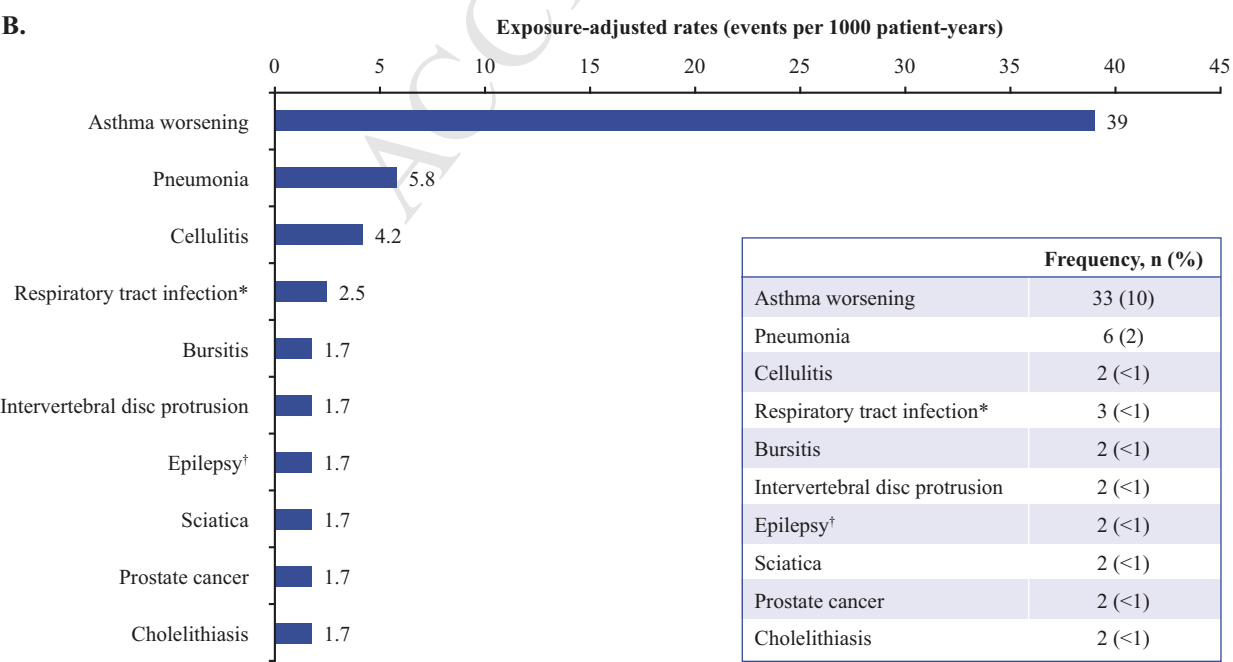
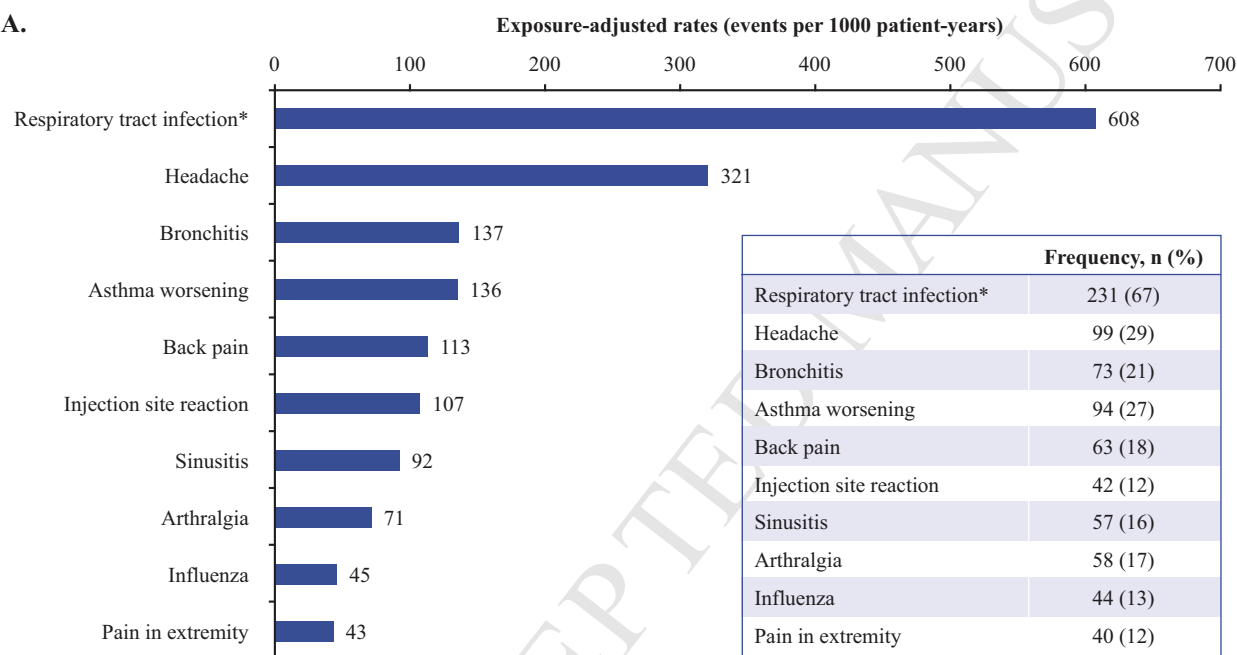
Pre-treatment refers to the 12 months prior to enrolment in DREAM.

ACQ-5 responder defined as patients with a reduction in ACQ-5 score of ≥0.5 points from baseline. Vertical bars show 95% confidence intervals. Minimum clinically important difference: ACQ-5, 0.5 points; FEV₁, 100 mL

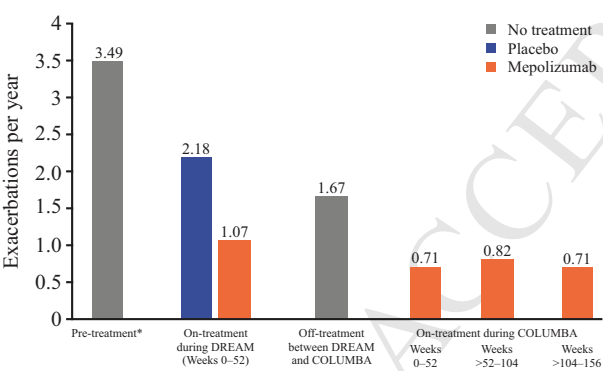
ACQ-5, Asthma Control Questionnaire-5; FEV₁, forced expiratory volume in 1 second.



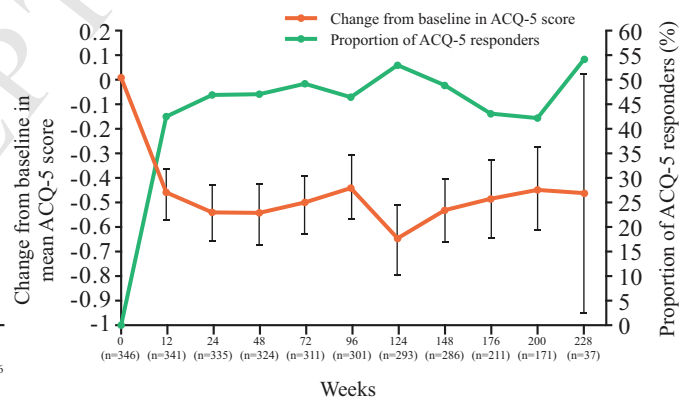




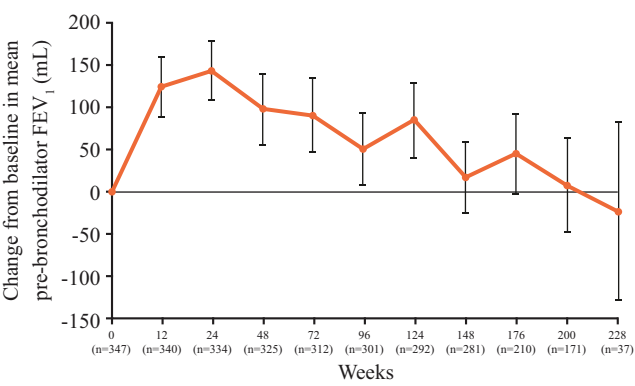
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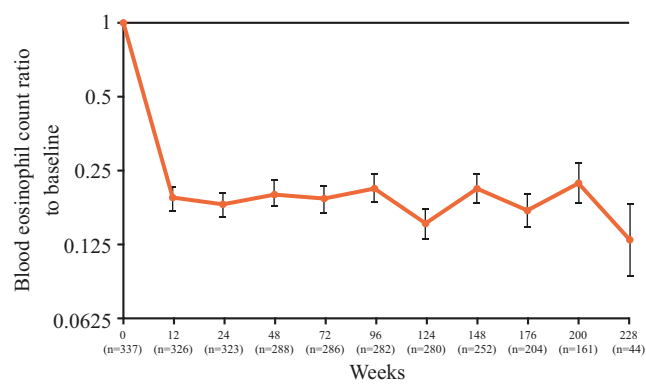
B.



C.



D.



Supplementary Materials

Further exclusion criteria

Patients were excluded from participation in COLUMBA if they had any of the following: severe or clinically significant cardiovascular disease uncontrolled with standard treatment, elevated liver function tests, any current malignancy or previous history of cancer in remission for <12 months prior to 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.

Adverse events of special interest

Within the mepolizumab clinical development program AEs include: systemic (allergic/hypersensitivity and non-allergic) 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 (SCS), hospitalization, or an emergency department visit. SCS comprised oral or intravenous corticosteroids for ≥ 3 days or a single intramuscular subcutaneous dose; for patients on maintenance SCS, at least double the existing maintenance dose was required for ≥ 3 days.

Participating countries

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

Supplementary Figure 1. Summary of (A) on-treatment AEs occurring in >10% of patients and (B) on-treatment SAEs occurring in >1 patient by age of asthma onset* (as treated population)

- represents AEs that were not reported in these populations.

*AEs were listed in line with Figure 3. [†]Respiratory tract infection encompasses all adverse events 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.

AE, adverse event; SAE, serious adverse event.

Supplementary Figure 2. Annualized rate of on-treatment exacerbations by baseline blood eosinophil count

Supplementary Table 1. Summary of AEs leading to patient withdrawal from trial or permanent discontinuation of study drug

AE leading to patient withdrawal	N (%)
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 cardiomyopathy	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	1 (<1)
Aspartate aminotransferase increased	1 (<1)
Gamma-glutamyltransferase increased	1 (<1)
Obesity	1 (<1)
Atopic dermatitis	1 (<1)

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

AE, adverse event.

Supplementary Table 2. Summary of on-treatment AEs* occurring in >10% of patients and on-treatment SAEs occurring in >1 patient by age of asthma onset (as treated population)

	Early onset, age <33 years (N=173)	Late onset, age ≥33 years (N=174)
On-treatment AEs, n (%)		
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, n (%)		
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 n (%), - represents AEs that were not reported in these populations

*AEs were listed in line with Figure 3. [†]Respiratory tract infection encompasses all adverse events 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.

AE, adverse event; SAE, serious adverse event.

Supplementary Table 3. Summary of the on-treatment AEs occurring in >10% of patients and on-treatment SAEs occurring in >1 patient by 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, n (%)		
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, n (%)		
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 n (%), - represents AEs that were not reported in these populations

*AEs were listed in line with Figure 3. [†]Respiratory tract infection encompasses all adverse events 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.

AE, adverse event; SAE, serious adverse event.

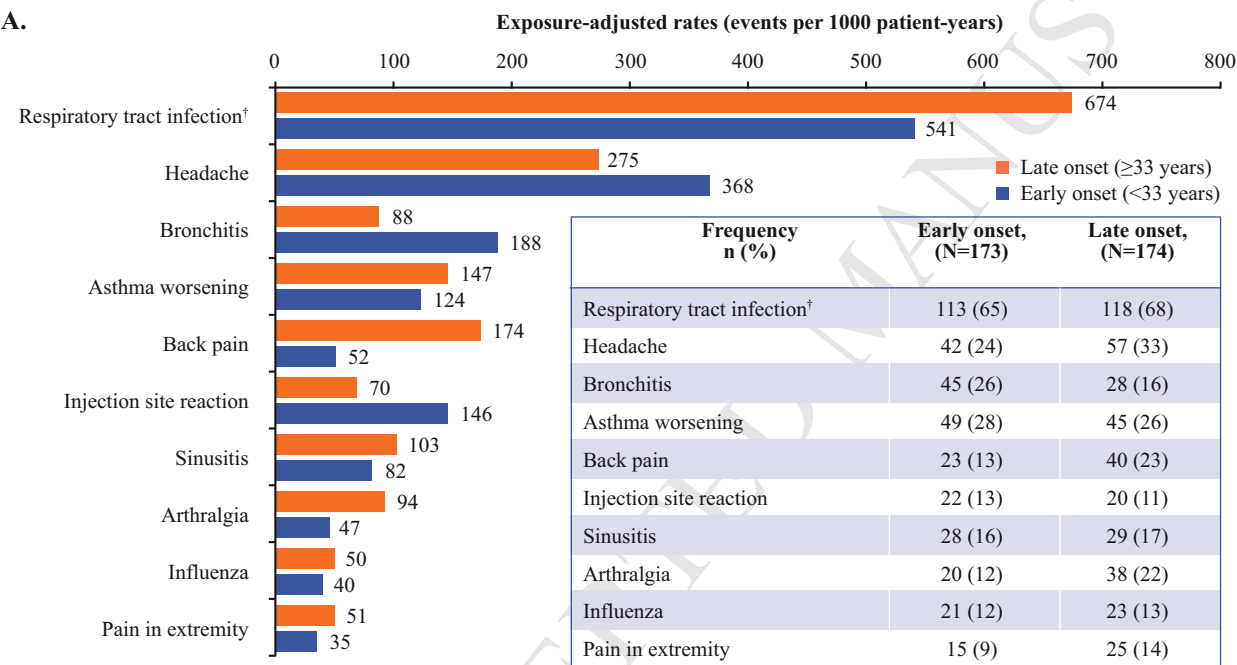
Supplementary Table 4. Overview of Exacerbation Rate per year across DREAM and COLUMBA

Treatment Period	Exacerbation Rate/Year		
	Placebo (n=77)	Mepolizumab (n=270)	Total (n=347)
Subjects with at least 52 weeks open label data	n=69	n=254	n=323
Pre-treatment*			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 at least 104 weeks open label data	n=62	n=240	n=302
Pre-treatment*			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 at least 156 weeks open label data	n=62	n=224	n=286
Pre-treatment*			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 at least 208 weeks open label data	n=39	n=131	n=170
Pre-treatment*			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

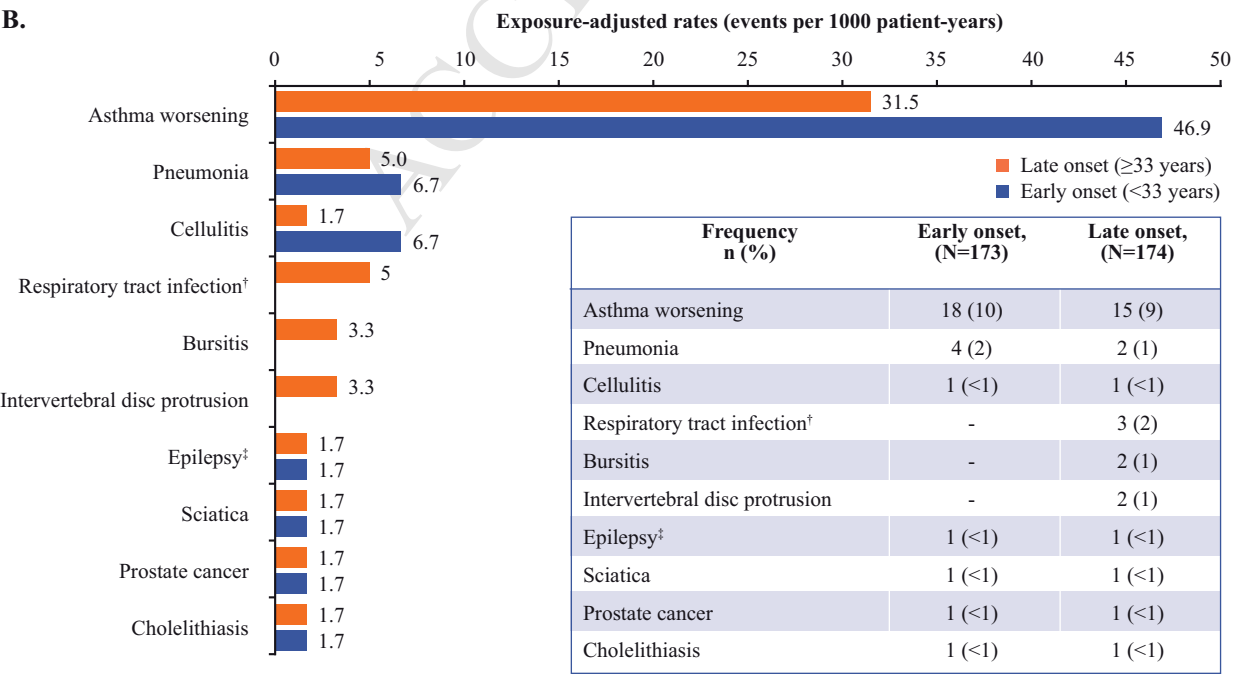
*12 months prior to enrolment in DREAM

[†]Week 0-52, double-blind phase of DREAM. Treatment included IV administered doses of mepolizumab (75mg, 250mg, 750mg) or placebo.[‡]Subjects were being treated with standard of care by investigators during this period.[¶]All subjects received open label mepolizumab 100mg SC during COLUMBA in addition to standard of care.

A.



B.



Exacerbations per year

