Long-term Safety and Clinical Benefit of Mepolizumab in Patients With the Most Severe Eosinophilic Asthma: The COSMEX Study

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ABSTRACT

Purpose: The goal of this study was to assess the long-term safety and efficacy of mepolizumab in patients with the most severe eosinophilic asthma.

Methods: This multicenter, open-label, long-term, Phase IIIb study (COSMEX [COSMOS Extension]; 201312/NCT02135692) enrolled patients from the 52-week, open-label extension study COSMOS (A Study to Determine Long-term Safety of Mepolizumab in Asthmatic Subjects) that previously enrolled patients from the double-blinded, placebo-controlled Phase III studies MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma) and SIRIUS (Steroid Reduction with Mepolizumab Study). To enter COSMEX, patients had to have life-threatening/seriously debilitating asthma before entering MENSA or SIRIUS and to have completed these previous studies with demonstrated improvement while receiving mepolizumab. In COSMEX, patients received mepolizumab 100 mg subcutaneously every 4 weeks as add-on therapy for up to 172 weeks. Primary endpoints were adverse event frequency and exacerbation rate per year; also assessed were forced

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expiratory volume in 1 s, Asthma Control Questionnaire-5 score, and daily oral corticosteroid (OCS) use.

Findings: Of the 340 patients enrolled, 339 received mepolizumab; median treatment duration within this extension study was 2.2 years, equating to 718 patient-years of additional exposure. No new safety signals were identified. Patients receiving mepolizumab throughout this study and previous studies had lasting reductions in exacerbation rate and daily OCS use and improvements in forced expiratory volume in 1 s and Asthma Control Questionnaire-5 score. In COSMEX, the on-treatment exacerbation rate (95% CI) was 0.93 (0.81−1.06) event/year for clinically significant exacerbations, 0.13 (0.10−0.18) event/year for exacerbations requiring hospitalization/emergency department visit, and 0.07 (0.05−0.10) event/year for exacerbations requiring hospitalization. In patients requiring systemic/oral corticosteroids with ≥128 weeks of continuous enrollment across SIRIUS, COSMOS, and COSMEX, mepolizumab maintained the median daily OCS dose at 1.3−2.8 mg during COSMEX, with additional patients no longer requiring OCS after extended mepolizumab treatment.

Implications: This study indicates that long-term mepolizumab treatment is well tolerated and associated with sustained clinical benefits in patients with severe eosinophilic asthma. ClinicalTrials.gov identifier: NCT02135692. (*Clin Ther*. 2019;41:2041−2056)

Key Words: asthma exacerbations, corticosteroids, long-term safety, mepolizumab, severe eosinophilic asthma.

INTRODUCTION

Asthma is a common, heterogeneous disease characterized by chronic airway inflammation, affecting an estimated 358 million people worldwide.[1−3] Patients with severe, persistent asthma comprise ~5%−10% of the total asthma population and represent a considerable health care burden as they have increased morbidity and mortality, frequently require hospitalization, and have high treatment costs.[4] There are several clinically recognized phenotypes of severe asthma, including severe eosinophilic asthma, which is characterized by elevated levels of peripheral eosinophils and frequent exacerbations.[5]

Mepolizumab, indicated for patients with severe eosinophilic asthma, is a humanized monoclonal antibody against interleukin-5.[6,7] It selectively inhibits eosinophilic inflammation[8,9] and reduces eosinophil levels in sputum and blood.[10] The safety and efficacy of mepolizumab have been investigated in several Phase III clinical trials. The MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma; NCT01691521) trial assessed the efficacy of subcutaneous (SC) and intravenous (IV) mepolizumab in patients with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high-dose inhaled corticosteroids (ICS). Mepolizumab significantly reduced asthma exacerbations by 53% (SC) and 47% (IV), and improved quality of life and asthma control, compared with placebo.[11] In the SIRIUS (Steroid Reduction with Mepolizumab Study; NCT01691508) trial, SC administration of mepolizumab resulted in a significant corticosteroid-sparing effect, reduced exacerbations by 32%, and improved control of asthma symptoms and quality of life compared with placebo in patients with severe eosinophilic asthma who required daily oral corticosteroid (OCS) therapy to maintain asthma control.[12] Findings from both studies also indicated that mepolizumab has a favorable safety profile.[11,12]

The long-term safety and efficacy of mepolizumab SC treatment in patients with severe eosinophilic asthma were also assessed in the COSMOS open-label extension study (NCT01842607).[13] This 52-week open-label extension study enrolled patients from the double-blind, placebo-controlled MENSA and SIRIUS studies, and showed that mepolizumab has a durable and stable response over an 18-month continuous treatment period, with reductions in exacerbation rate and OCS dosing maintained throughout the COSMOS study period.

Given the considerable burden of severe eosinophilic asthma, both in terms of health care costs and health-related quality of life, it is important to identify suitable and predictable management approaches for patients. The aim of the current study, COSMEX (COSMOS Extension), was to extend the findings of the MENSA, SIRIUS, and COSMOS studies. We

investigated the long-term safety and clinical efficacy of mepolizumab in a subset of patients with the most severe forms of severe eosinophilic asthma who had previously displayed improved disease control while receiving mepolizumab as add-on therapy.

PATIENTS AND METHODS

Study Design

COSMEX (201312/NCT02135692) was a multicenter, open-label, long-term, Phase IIIb study of mepolizumab in a subset of patients with the most severe forms of severe eosinophilic asthma (specifically a history of life-threatening or seriously debilitating asthma; definitions are given in the following section and in Table I). The study was conducted at 116 centers in 18 countries (see the Supplemental Material in the online version at doi:10.1016/j.clinthera.2019.07.007) between May 29, 2014, and October 5, 2017, and completed after all patients met a protocol-defined discontinuation criterion. Mepolizumab 100 mg SC was administered approximately every 4 weeks for up to 172 weeks. Patients continued to receive standard-of-care asthma therapy for the duration of the study, which could be adjusted at the physicians' discretion. After study completion, patients could enter another mepolizumab study (201810/NCT02555371 or 201956/NCT02543112) or receive mepolizumab commercially outside of a clinical trial, if locally available.

The study was approved by the appropriate regulatory and ethics committees and was performed in accordance with the Declaration of Helsinki 2008 and Good Clinical Practice guideline. Written

Table I. Description of study population in COSMEX (COSMOS Extension).

Most Severe Forms of Severe Eosinophilic Asthma*	Definitions for COSMEX Study	Additional Eligibility Criteria Required for Patient Enrollment
Life-threatening asthma	At least 1 of: • History of ≥1 intubation during their lifetime • ≥1 Hospitalization for asthma exacerbation within the 12 mo before MENSA or SIRIUS screening • ≥3 Exacerbations in the 12 mo before screening in MENSA • An optimized OCS dose (prednisone equivalent) of ≥10 mg at SIRIUS randomization	• Must have been receiving ICS controller medication (fluticasone propionate ≥500 μg/d or equivalent) for the previous 8 mo • *And* must have previously demonstrated a protocol-defined clinical benefit (see the Supplemental Material in the online version at doi:10.1016/j.clinthera.2019.07.007) from mepolizumab within the MENSA, SIRIUS, or COSMOS studies
Seriously debilitating asthma	• Percent-predicted FEV_1 of ≤50% at randomization for MENSA or SIRIUS • *And* either an ACQ-5 score ≥3 or SGRQ total score ≥60 at MENSA or SIRIUS randomization	

ACQ-5 = Asthma Control Questionnaire-5; COSMOS = A Study to Determine Long-term Safety of Mepolizumab in Asthmatic Subjects; FEV_1 = forced expiratory volume in 1 s; ICS = inhaled corticosteroids; OCS = oral corticosteroids; SGRQ = St. George's Respiratory Questionnaire.

* Patients were required to meet the definition of having life-threatening asthma or seriously debilitating asthma based on the health status of each patient before MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma) or SIRIUS (Steroid Reduction with Mepolizumab Study).

informed consent was obtained from each patient before study participation.

Patients

Patients with the most severe forms of severe eosinophilic asthma (eg, a history of life-threatening or seriously debilitating asthma) were enrolled from the COSMOS study (MEA115661/NCT01842607).[13] Before COSMOS, patients had completed either MENSA (MEA115588/NCT01691521)[11] or SIRIUS (MEA115575/NCT01691508)[12] (Figure 1). For the MENSA and SIRIUS studies, patients had severe eosinophilic asthma and required high-dose ICS with additional controller(s) and a blood eosinophil level ≥150 cells/μL at the initiation of treatment or ≥300 cells/μL during the year before study start. Regarding COSMEX entry eligibility, patients must have been receiving ICS controller medication (fluticasone propionate ≥500 μg/d or equivalent) for the previous 8 months and must have previously reported a protocol-defined clinical benefit (see the Supplemental Material in the online version at doi:10.1016/j.clinthera.2019.07.007) from mepolizumab within the MENSA, SIRIUS, or COSMOS studies.

When identifying the most severe forms of severe eosinophilic asthma for COSMEX, "life-threatening" asthma was defined as history of ≥1 intubation during the patient's lifetime, ≥1 hospitalization for asthma exacerbation within the 12 months before MENSA or SIRIUS screening, and ≥3 exacerbations in the 12 months before MENSA screening or an optimized OCS dose (prednisone equivalent) ≥10 mg at SIRIUS randomization. "Seriously debilitating" asthma was defined as percent-predicted forced expiratory volume in 1 s (FEV_1) ≤50% and either an Asthma Control Questionnaire-5 (ACQ-5)

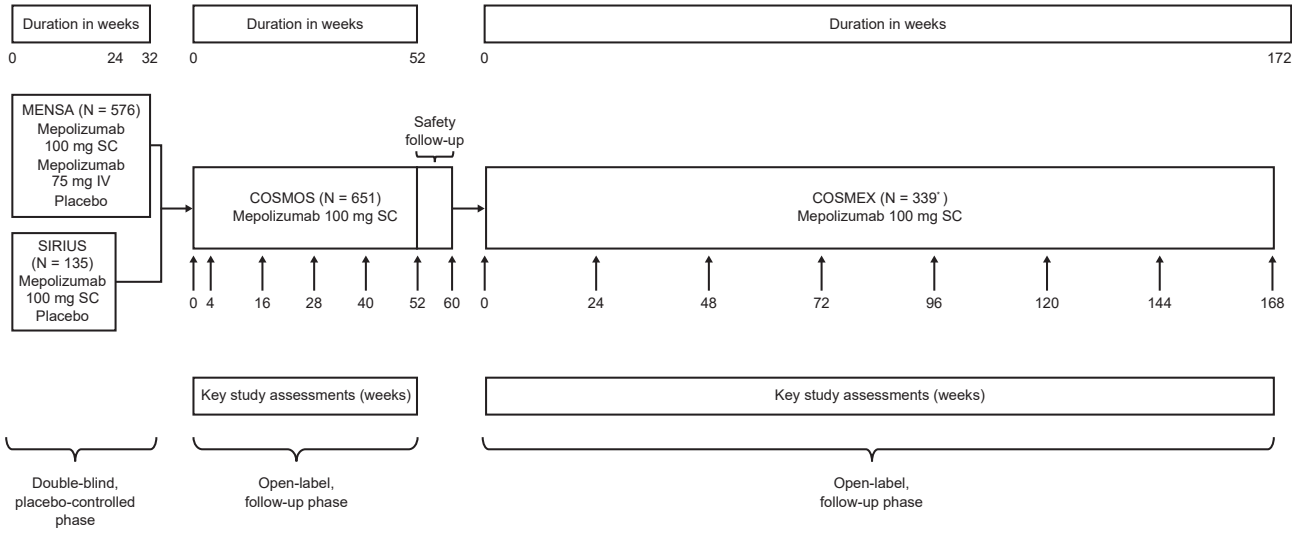


Figure 1. Duration and patient contribution to the COSMEX (COSMOS Extension) study. Overall, the COSMEX mepolizumab-responsive patient population comprised 22% (73 of 339) of patients from SIRIUS (Steroid Reduction with Mepolizumab Study) and 78% (266 of 339) of patients from MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma); 54% (73 of 135) of patients from SIRIUS were enrolled, and 46% (266 of 576) of patients from MENSA were enrolled. The safety follow-up period after COSMOS (A Study to Determine Long-term Safety of Mepolizumab in Asthmatic Subjects) was not required for patients enrolling immediately into COSMEX. After completion of COSMEX, patients could enter a further mepolizumab study (201810 or 201956) or receive mepolizumab commercially outside of a clinical trial, if locally available. *One patient failed screening (see the Supplemental Material in the online version at doi:10.1016/j.clinthera.2019.07.007). IV = intravenous; SC = subcutaneous.

score ≥3 or St. George's Respiratory Questionnaire total score ≥60 at MENSA or SIRIUS randomization. Exclusion criteria are listed in the Supplemental Material in the online version at doi:10.1016/j.clinthera.2019.07.007.

There was a treatment gap of varying length between COSMOS and COSMEX. Because the effect of mepolizumab wanes ~3 months after stopping treatment (leading to a rise in eosinophil levels), patients were stratified into 2 groups for analysis: those with a treatment interval ≤12 weeks (continuous therapy group) or >12 weeks (interrupted therapy group) between COSMOS and COSMEX.

Endpoints

The primary safety endpoint was the frequency of adverse events (AEs), serious AEs (SAEs), and AEs of special interest (see the Supplemental Material in the online version at doi:10.1016/j.clinthera.2019.07.007). Deaths from any cause and selected cardiovascular events were adjudicated by a Clinical Endpoint Committee. Secondary safety endpoints included the number of withdrawals due to AEs or lack of efficacy, and the frequency of positive anti−mepolizumab-binding antibodies and of neutralizing antibodies. A tiered testing approach was used for immunogenicity analyses, which involved screening and confirmation of antidrug antibodies (using a binding antibody assay), followed by titration and analysis of neutralizing antibodies (using an indirect ligand-binding assay). Samples were diluted with an anti−interleukin-5 blocking antibody and incubated with biotin and ruthenium drug conjugates; a screening cut-point was used, which was statistically calculated to achieve a 5% false-positive response rate. Positive antidrug antibody samples were confirmed by repeating the analyses in the presence of excess drug; a 1% false-positive rate was used for confirmation. Positive antidrug antibody samples were subsequently tested for the presence of neutralizing antibodies; a 1% false-positive neutralizing antibody cut-point was used for confirmation.

The annualized rate of exacerbations was the primary efficacy endpoint. An exacerbation was defined as a worsening of asthma that required systemic corticosteroids, hospitalization, or an emergency department visit. Systemic corticosteroids comprised OCS or IV corticosteroids for ≥3 days or a single intramuscular corticosteroid dose; for patients on maintenance systemic corticosteroids, at least double the existing maintenance dose was required for ≥3 days. Secondary efficacy endpoints included ACQ-5 score and pre-bronchodilator FEV_1 over the study period. OCS use was summarized for those patients who had participated in the SIRIUS study.

Statistical Analysis

No sample size calculations were required for this study: this factor was determined by the number of available and eligible patients who were enrolled in COSMOS. All analyses were performed by using data from patients who received at least 1 dose of open-label mepolizumab within COSMEX.

The proportion of patients reporting AEs was summarized by using the Medical Dictionary for Regulatory Activities Primary System Organ Class (SOC) and preferred term. Exposure-adjusted AE rates were presented to account for the length of exposure within COSMEX and to allow for comparisons versus previous mepolizumab studies. Annualized rate of asthma exacerbations was analyzed by using a negative binomial generalized linear model, with logarithm of time on treatment included as an offset variable. Exacerbations separated by < 7 days were treated as a continuation of the same exacerbation. All endpoints were summarized by using appropriate descriptive statistics (mean/geometric mean, median, SD, and range). For blood eosinophil counts, if a result of zero was recorded, a small value (ie, one half the minimum non-zero result) was imputed before log-transformation. All statistical analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Patient Population

Description of patient entry into COSMEX from the MENSA, SIRIUS, and COSMOS studies is shown in Figure 1. In total, 340 patients were enrolled in COSMEX, and 339 received treatment with open-label mepolizumab (1 patient was excluded because they had not had an exacerbation during MENSA

while on placebo, and they therefore failed the exacerbation history criterion for COSMEX) (see the Supplemental Material in the online version at doi:10.1016/j.clinthera.2019.07.007). All patients previously received mepolizumab 100 mg SC in the COSMOS study, and the majority (78%) had previously participated in the MENSA study. Demographic and baseline characteristics of the study population are shown in Table II. The median duration of mepolizumab treatment in the COSMEX study was 2.2 years (range, 8 weeks−3.3 years), equating to 718 patient-years of exposure (Table II). The total exposure in the 339 patients studied across MENSA, SIRIUS, COSMOS, and COSMEX was 1202 patient-years, with a maximum exposure duration of 4.8 years.

Seventy-five percent of patients had ≤12 weeks between the last dose in COSMOS and the first dose in COSMEX. For those patients with a prolonged gap in treatment between studies (>12 weeks between doses), a statistically significant increase in ACQ-5 score and blood eosinophil levels, and a clinically important decrease in lung function, were observed at baseline compared with those who had ≤12 weeks between doses (Table II). There were no differences in concomitant medication use between the continuous and interrupted mepolizumab groups (Table II); all patients continued to receive background standard-of-care asthma medications throughout.

All 339 patients had discontinued by study conclusion; almost one half (47% [159 of 339]) remained in the study until mepolizumab became commercially available in their country, and 45% (153 of 339) of patients discontinued because the study was closed/terminated in their country. The most common reasons for withdrawal before mepolizumab became commercially available or study closure were withdrawal of consent (4% [15 of 339]), lost to follow-up (1% [4 of 339]), and AEs (1% [4 of 339]) (see Supplemental Table I in the online version at doi:10.1016/j.clinthera.2019.07.007). There was a low dropout rate in the first year, after which the dropout rate increased as patients left the study due to the country-specific commercial availability of mepolizumab as per the protocol-defined stopping criteria (see the Supplemental Figure 1 in the online version at doi:10.1016/j.clinthera.2019.07.007).

Safety

Overall, 315 (93%) patients reported on-treatment AEs; 51 (15%) experienced an AE that was considered by the investigator to be treatment related. Four (1%) patients were withdrawn from the study due to AEs (patient 1, asthma exacerbation, anxiety disorder, and neurodermatitis; patient 2, elevated liver function test result; patient 3, musculoskeletal pain; and patient 4, severe asthma exacerbation with fatal multiple organ dysfunction and systemic inflammatory response) (see the Supplemental Material in the online version at doi:10.1016/j.clinthera.2019.07.007). Two patients (0.6%) were withdrawn due to lack of efficacy (see Supplemental Table 1 in the online version at doi:10.1016/j.clinthera.2019.07.007). Eighty-four (25%) patients experienced SAEs during treatment, of whom 3 (0.9%) experienced an SAE that was considered by the investigator to be treatment related. The most common on-treatment SAE was asthma (exacerbation), which occurred in 34 (10%) patients, with other SAEs occurring at a lower frequency (Figure 2). Pneumonia was the only other on-treatment SAE to occur in >1% of patients, occurring in 6 (2%) patients. Pneumonia was confirmed by radiograph, computerized tomography scan, or sputum culture.

On-treatment AEs of special interest are summarized in Table III. Two (<1%) patients experienced investigator-defined systemic reactions, both of which were considered hypersensitivity reactions related to mepolizumab. The first patient reported malaise with headache, and the second reported dizziness with light-headedness. Both were nonserious and mild to moderate in intensity, reportedly have resolved, and did not lead to mepolizumab discontinuation. No nonallergic systemic reactions or mepolizumab-related anaphylaxis were reported. Two patients reported anaphylaxis considered unrelated to mepolizumab by the investigator; mepolizumab was continued in both cases. Injection-site reactions were reported by 14 (4%) of 339 patients. Patients with events potentially representing opportunistic infections involved *Herpes* (n = 8), *Candida* (n = 3), and pulmonary tuberculosis (n = 1). Three additional patients also reported *Herpes zoster* infections, all of which were nonserious and resolved with continued mepolizumab

Table II. Patient demographic characteristics, baseline characteristics, and treatment exposure. Continued and interrupted groups reflect patients with a treatment interval ≤12 weeks and >12 weeks, respectively, between COSMOS (A Study to Determine Long-term Safety of Mepolizumab in Asthmatic Subjects) and COSMEX (COSMOS Extension).

Parameter	Mepolizumab 100 mg SC Continued (n = 254)	Mepolizumab 100 mg SC Interrupted (n = 85)	Mepolizumab 100 mg SC (n = 339)
Demographic and baseline characteristics*			
Female	128 (50)	50 (59)	178 (53)
Age, mean (SD), y	53.4 (13.0)	51.5 (13.2)	52.9 (13.1)
Race, no. (%)			
White	205 (81)	79 (93)	284 (84)
Asian	49 (19)	2 (2)	51 (15)
African-American/African heritage	0 (0)	4 (5)	4 (1)
Ethnicity, Hispanic/Latino, no. (%)	6 (2)	12 (14)	18 (5)
ACQ-5 score,† mean (SD)	n = 252	n = 85	n = 337
	1.38 (1.09)	2.26 (1.35)	1.60 (1.22)
Pre-bronchodilator FEV_1, mean (SD), L	n = 252	n = 84	n = 336
	1.995 (0.753)	1.892 (0.675)	1.969 (0.734)
Percent predicted pre-bronchodilator FEV_1,	n = 252	n = 84	n = 336
mean (SD)	64.5 (18.1)	61.6 (18.5)	63.8 (18.2)
Blood eosinophil count, cells/μL,	n = 246	n = 76	n = 322
geometric mean (SD logs)	50 (0.93)	260 (1.13)	80 (1.19)
Concurrent therapy, no. (%) (COSMEX)			
Inhaled corticosteroid	247 (97)	82 (96)	329 (97)
Long-acting $beta_2$- agonist	250 (98)	82 (96)	332 (98)
Short-acting $beta_2$- agonist	213 (84)	67 (79)	280 (83)
Leukotriene receptor antagonist	117 (46)	34 (40)	151 (45)
Long-acting muscarinic antagonist	57 (22)	19 (22)	76 (22)
Xanthine	61 (24)	11 (13)	72 (21)
Interval between COSMOS and COSMEX study dosing			
Interval between COSMOS and COSMEX study dosing, median (range), wk	4.1 (1−12)	27.3 (12−40)	5.0 (1−40)
Interval period between COSMOS and COSMEX study dosing, no. (%)			
≤4 wk	112 (44)	0	112 (33)
>4−≤8 wk	106 (42)	0	106 (31)
>8−≤12 wk	36 (14)	0	36 (11)
>12−≤16 wk	0	13 (15)	13 (4)
>16−≤20 wk	0	8 (9)	8 (2)
>20−≤24 wk	0	11 (13)	11 (3)
>24 wk	0	53 (62)	53 (16)
Mepolizumab exposure (COSMEX)			
Time on treatment, median (range), mo	—	—	26.8 (2−39)

(*continued on next page*)

Table II. (*Continued*)

Parameter	Mepolizumab 100 mg SC Continued (n = 254)	Mepolizumab 100 mg SC Interrupted (n = 85)	Mepolizumab 100 mg SC (n = 339)
Total patient-years exposure	—	—	718.38
Period of exposure, no. (%)			
≥6 mo	—	—	333 (98)
≥12 mo	—	—	328 (97)
≥24 mo	—	—	197 (58)
≥36 mo	—	—	31 (9)
Mepolizumab exposure (MENSA, SIRIUS, COSMOS, and COSMEX)			
Time on treatment, median (range), mo	—	—	42.9 (14–57)
Total patient-years exposure	—	—	1201.93
Period of exposure, no. (%)			
≥12 mo	—	—	339 (100)
≥24 mo	—	—	333 (98)
≥36 mo	—	—	262 (77)
≥48 mo	—	—	128 (38)

ACQ-5 = Asthma Control Questionnaire-5; FEV_1 = forced expiratory volume in 1 s; MENSA = Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma; SC = subcutaneous; SIRIUS = Steroid Reduction with Mepolizumab Study.
* The demographic and baseline characteristics section presents patients' characteristics when commencing COSMEX (COSMOS Extension).
† Lower scores reflect greater asthma control.

treatment. Malignancies were reported in 8 (2%) patients: basal cell carcinoma (n = 2), prostate cancer (n = 2), breast cancer (n = 1), colon adenocarcinoma (n = 1), colon neoplasm (n = 1), and melanoma (n = 1). Five investigator-reported nonfatal cardiovascular events were reviewed by the Clinical Endpoint Committee; of these, 3 patients had events adjudicated as cardiovascular (myocardial infarction in all 3 patients).

Overall, 2 fatalities were reported and adjudicated by the Clinical Endpoint Committee, one as respiratory and the other as cardiovascular; neither death was considered related to mepolizumab by the investigator (details are given in the Supplemental Material in the online version at doi:10.1016/j.clinthera.2019.07.007). In total, 335 patients were tested for the presence of anti-mepolizumab antibodies after the first mepolizumab dose within COSMEX; 6 (2%) had anti-mepolizumab antibodies at least once postbaseline with no neutralizing antibodies detected. No relationship between the frequency of AEs or hypersensitivity reactions and the presence or absence of antidrug antibodies was observed.

Efficacy

In total, 215 (63%) of 339 patients experienced 658 on-treatment exacerbations over the on-treatment period (median duration, 2.2 years; range, 8 weeks–3.3 years). The annualized on-treatment exacerbation rate (95% CI) was 0.93 (0.81–1.06) event/year. The annualized rate of on-treatment exacerbations requiring hospitalization or an emergency department visit was 0.13 (0.10–0.18) event/year and 0.07 (0.05–0.10) event/year for those requiring hospitalization. Those patients with continuous study participation since MENSA reported a sustained reduction in exacerbation rate with prolonged mepolizumab treatment throughout multiple studies (MENSA, COSMOS, and COSMEX) (Figure 3).

Patients with a treatment gap >12 weeks between COSMOS and COSMEX reported a worsening of

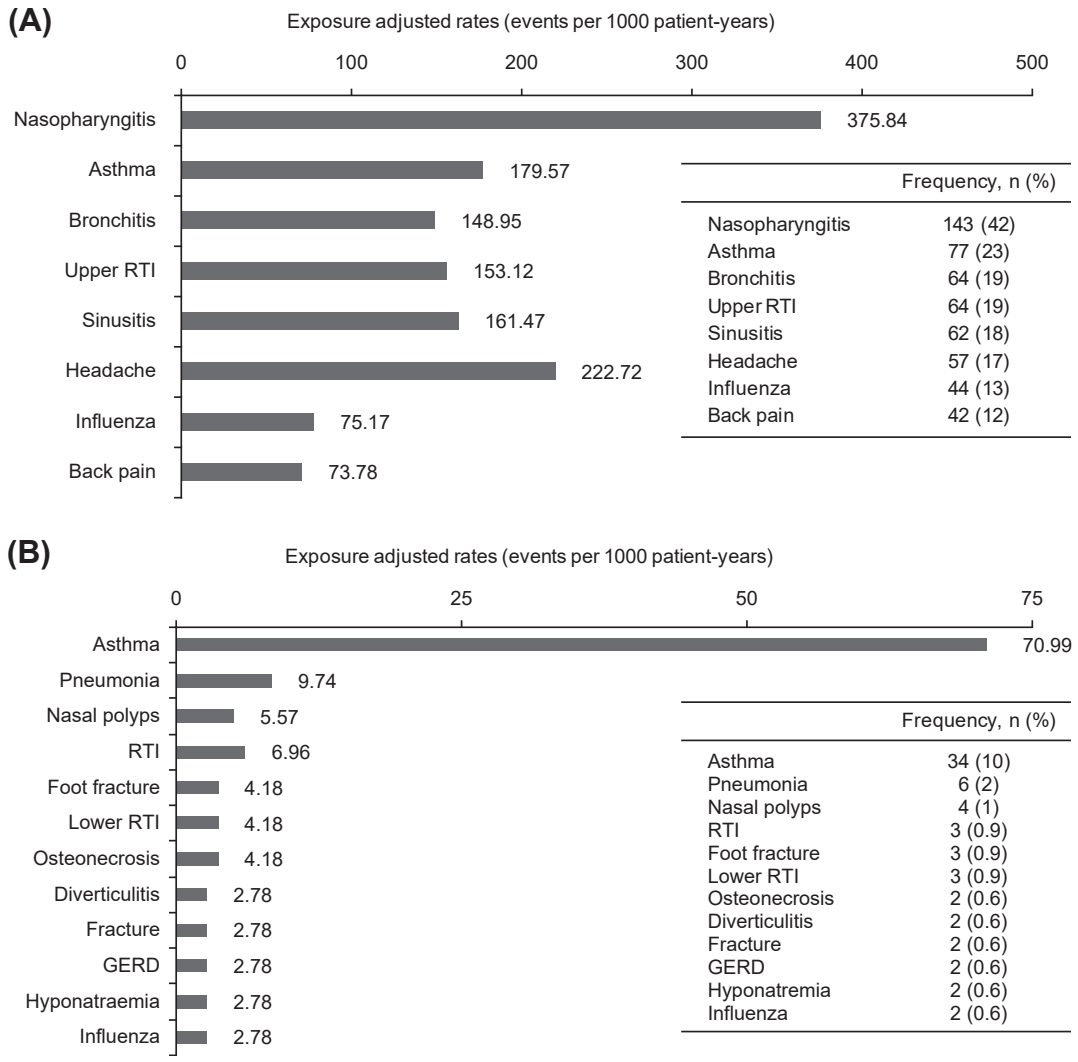


Figure 2. Summary of (A) on-treatment adverse event (AEs) occurring in >10% of patients and (B) on-treatment serious AEs occurring in >1 patient. GERD = gastroesophageal reflux disease; RTI = respiratory tract infection.

their asthma; however, after re-starting mepolizumab, patients experienced improvements in asthma control as measured according to the ACQ-5 score (Figure 4A). There was also a slight improvement in lung function as measured by using FEV_1 (Figure 4B) and a marked reduction in blood eosinophil levels after re-introduction of mepolizumab (Figure 4C). Patients with continuous mepolizumab treatment presented limited changes in efficacy parameters, reflecting a continuation of the benefits observed with mepolizumab treatment in previous studies. Those patients who had continuous study participation since the corticosteroid-sparing SIRIUS study (and therefore required OCS before randomization in SIRIUS) exhibited a sustained reduction in daily OCS usage with prolonged mepolizumab treatment throughout multiple studies (SIRIUS, COSMOS, and COSMEX) (Figure 5; see Supplemental Table II in the online version at doi:10.1016/j.clinthera.2019.07.007). In addition, 17 (45%) of 38 patients with

Table III. Summary of on-treatment adverse events of special interest. Values are given as no. (%).

Adverse Event	Mepolizumab 100 mg SC (N = 339)
Systemic reactions*	2 (0.6)
Allergic/hypersensitivity reactions	2 (0.6)
Nonallergic reactions	0
Anaphylaxis†	0
Local injection-site reactions*	14 (4)
All infections‡	282 (83)
Serious infections	20 (6)
Opportunistic infections§	15 (4)
Neoplasms‡	20 (6)
Malignancies‖	8 (2)
Cardiac disorders‡	15 (4)
Serious cardiac disorders	6 (2)
Serious CVT events¶	7 (2)
Serious ischemic events#	3 (0.9)

CVT = cardiac, vascular and thromboembolic; SC = subcutaneous.
* As identified by the investigator in electronic case report form designed for collecting data on systemic reactions or local injection-site reactions.
† Considered by the investigator to represent a systemic reaction meeting Sampson's criteria (Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391–397) for anaphylaxis.
‡ All infections included all events in Infections and infestations System Organ Class (SOC); neoplasms include all events in Neoplasms benign malignant and unspecified (including cysts and polyps) SOC; cardiac disorders includes all events in Cardiac disorders SOC.
§ 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 (Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. *Ann Rheum Dis*. 2015;74:2107–211).
‖ All neoplasms were identified from Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC and standard Medical Dictionary for Regulatory Activities (MedDRA) queries.
¶ All serious CVT events were identified from Cardiac Disorders SOC, Vascular Disorders SOC, and standard MedDRA queries.
# Subset of serious CVT events was identified through standard MedDRA queries.

≥128 weeks of continuous reporting across SIRIUS, COSMOS, and COSMEX no longer required OCS treatment between weeks 124 and 128, and 7 (58%) of 12 patients with data up to 232 weeks no longer required OCS between weeks 228 and 232 (see Supplemental Table III in the online version at doi:10.1016/j.clinthera.2019.07.007).

DISCUSSION

In selected patients with the most severe forms of severe eosinophilic asthma who had previously shown clinical benefit with mepolizumab, long-term treatment with mepolizumab throughout COSMEX and previous lead–in studies was well tolerated and provided sustained and consistent reductions in exacerbation rate, with sustained improvements in ACQ-5 score and FEV_1 over a period of up to 4.5 years. Furthermore, the reduction in OCS dose initially achieved during SIRIUS was also sustained, with additional patients no longer requiring OCS treatment following continued mepolizumab treatment across the SIRIUS, COSMOS, and COSMEX studies. This study extends our knowledge of the long-term safety and efficacy of mepolizumab

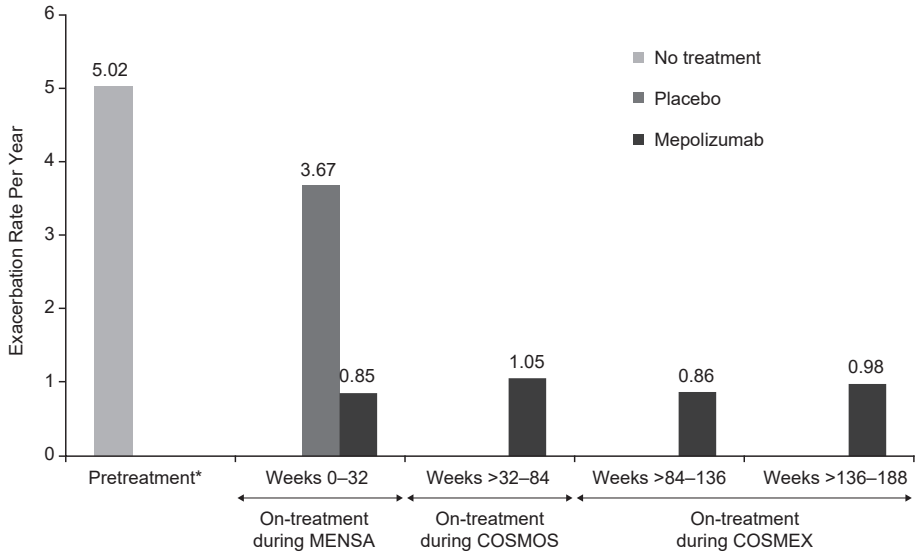
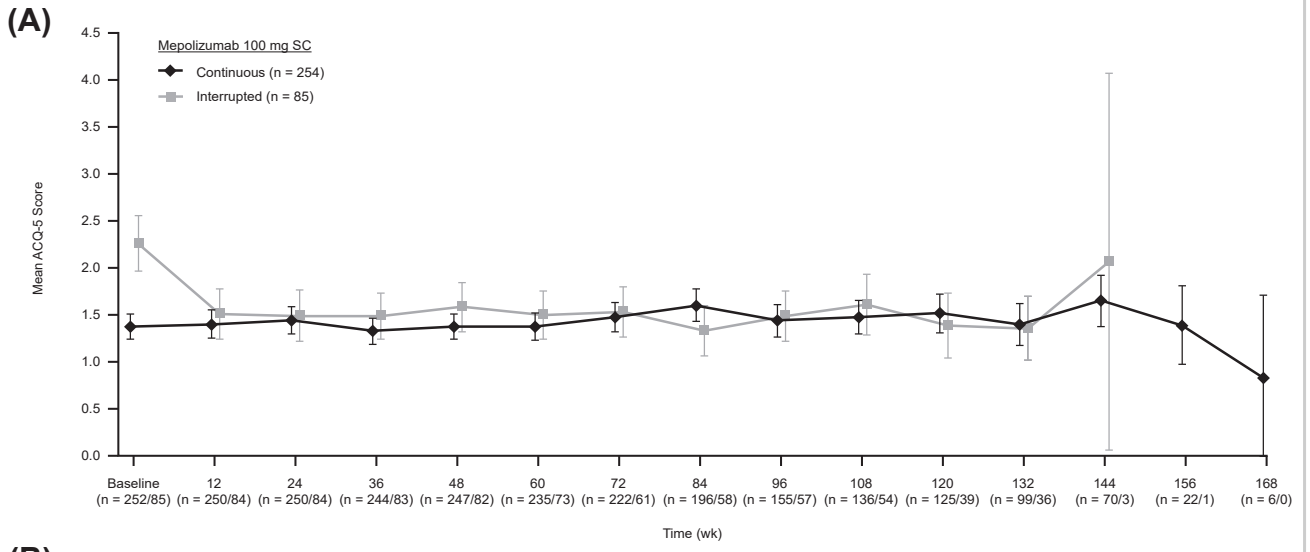


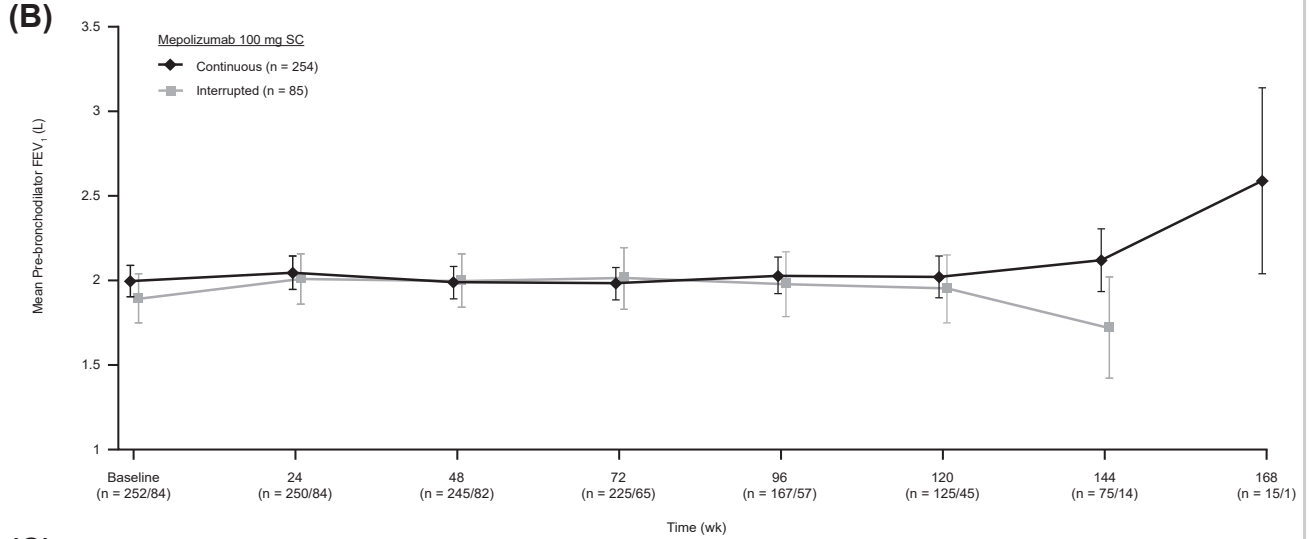
Figure 3. Exacerbation rate per year throughout the MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma), COSMOS (A Study to Determine Long-term Safety of Mepolizumab in Asthmatic Subjects), and COSMEX (COSMOS Extension) studies in patients with ≥188 weeks of continuous enrollment. In total, 95 patients with ≥188 weeks of continuous reporting across MENSA, COSMOS, and COSMEX with ≤12 weeks between the last dose in COSMOS and first dose in COSMEX are summarized (MENSA, placebo, n = 24; mepolizumab, n = 71). The mepolizumab group in MENSA contains patients on both 100 mg SC and 75 mg IV doses. Analyses include clinically significant exacerbations from MENSA and all exacerbations from COSMOS and COSMEX. *Pretreatment refers to the 12 months before enrollment in MENSA.

in a population of patients with the most severe forms of eosinophilic asthma.

The type and frequency of the AEs, including fatal events and events of special interest, reported in this study were broadly consistent with those reported in other mepolizumab clinical studies,[11–15] and no new safety concerns were identified. Immunogenicity incidence was low and consistent with previous mepolizumab studies in severe eosinophilic asthma, and no patients tested positive for neutralizing antibodies [11–15].

The primary efficacy endpoint for this study was the annualized exacerbation rate, which was estimated at 0.93 event/year, consistent with findings from the COSMOS and COLUMBA (Open-label Long Term Extension Safety Study of Mepolizumab in Asthmatic Subjects; MEA115666/NCT01691859) mepolizumab studies in which rates of 0.93 and 0.68 event/year, respectively, were reported.[13,16] In addition, those patients with continuous study participation since MENSA reported a sustained reduction in exacerbation rate with mepolizumab. Patients with ≥188 weeks of continuous enrollment across MENSA, COSMOS, and COSMEX presented an annualized exacerbation rate of ~5 events/year in the 12 months before MENSA, which was reduced by mepolizumab to ~1 event/year across studies. There were limited changes in efficacy parameters (ACQ-5 and FEV_1) in COSMEX, demonstrating the persistence of clinical benefit in responsive patients treated continuously with mepolizumab with no sign of loss of efficacy. The withdrawal rate due to a lack of efficacy was very low, further supporting the durability of mepolizumab. Furthermore, we observed that long-term mepolizumab treatment provided a sustained OCS reduction and no evidence of tolerance to mepolizumab after long-term administration, with blood eosinophil levels remaining low and stable.


(A)
Mepolizumab 100 mg SC
Continuous (n = 254)
Interrupted (n = 85)
Mean ACQ-5 Score
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Baseline (n = 252/85)
12 (n = 250/84)
24 (n = 250/84)
36 (n = 244/83)
48 (n = 247/82)
60 (n = 235/73)
72 (n = 222/61)
84 (n = 196/58)
96 (n = 155/57)
108 (n = 136/54)
120 (n = 125/39)
132 (n = 99/36)
144 (n = 70/3)
156 (n = 22/1)
168 (n = 6/0)
Time (wk)


(B)
Mepolizumab 100 mg SC
Continuous (n = 254)
Interrupted (n = 85)
Mean Pre-bronchodilator FEV1 (L)
3.5
3
2.5
2
1.5
1
Baseline (n = 252/84)
24 (n = 250/84)
48 (n = 245/82)
72 (n = 225/65)
96 (n = 167/57)
120 (n = 125/45)
144 (n = 75/14)
168 (n = 15/1)
Time (wk)

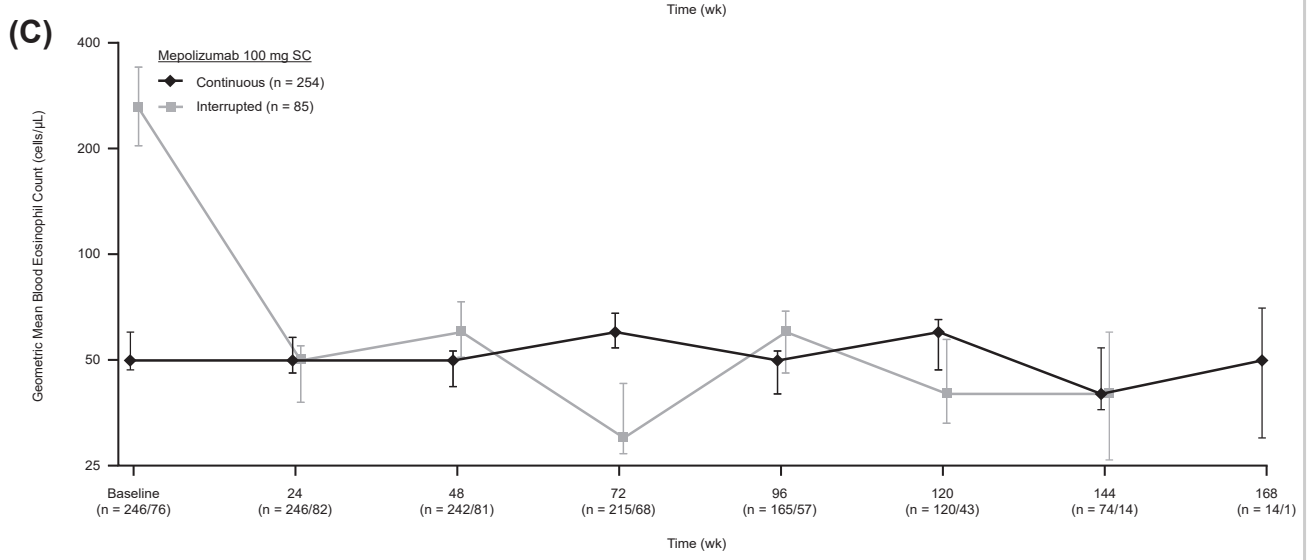

(C)
Mepolizumab 100 mg SC
Continuous (n = 254)
Interrupted (n = 85)
Geometric Mean Blood Eosinophil Count (cells/μL)
400
200
100
50
25
Baseline (n = 246/76)
24 (n = 246/82)
48 (n = 242/81)
72 (n = 215/68)
96 (n = 165/57)
120 (n = 120/43)
144 (n = 74/14)
168 (n = 14/1)
Time (wk)

Figure 4. On-treatment absolute values in (A) Asthma Control Questionnaire-5 (ACQ-5) score, (B) pre-bronchodilator forced expiratory volume in 1 s (FEV_1), and (C) peripheral blood eosinophil count in patients receiving continuous compared with interrupted mepolizumab treatment in COSMEX (COSMOS Extension). Values have not been displayed when n = 1. Error bars represent 95% CIs. Continued and interrupted groups reflect patients with a treatment interval of ≤12 weeks and >12 weeks, respectively, between COSMOS (A Study to Determine Long-term Safety of Mepolizumab in Asthmatic Subjects) and COSMEX. SC = subcutaneous.

Although most patients enrolled in COSMEX had minimal gaps between successive clinical studies, a small proportion experienced a prolonged interruption in mepolizumab treatment (>12 weeks between COSMOS and COSMEX doses). These patients showed a worsening in lung function (FEV_1) and asthma control (ACQ-5 score) and an increase in blood eosinophil count at baseline compared with patients who had maintained continuous therapy. These data are consistent with the long-term COLUMBA safety study, in which the cessation of mepolizumab led to increases in blood eosinophil levels and frequency of exacerbations approaching pretreatment levels.[16] In severe eosinophilic asthma, frequent exacerbations have been associated with a loss in lung function, compared with those with no or infrequent exacerbations.[17–19] In addition, another study also showed that cessation of mepolizumab resulted in significant between-visit increases in blood eosinophil count at 0–3 months, and at 3–6 months,

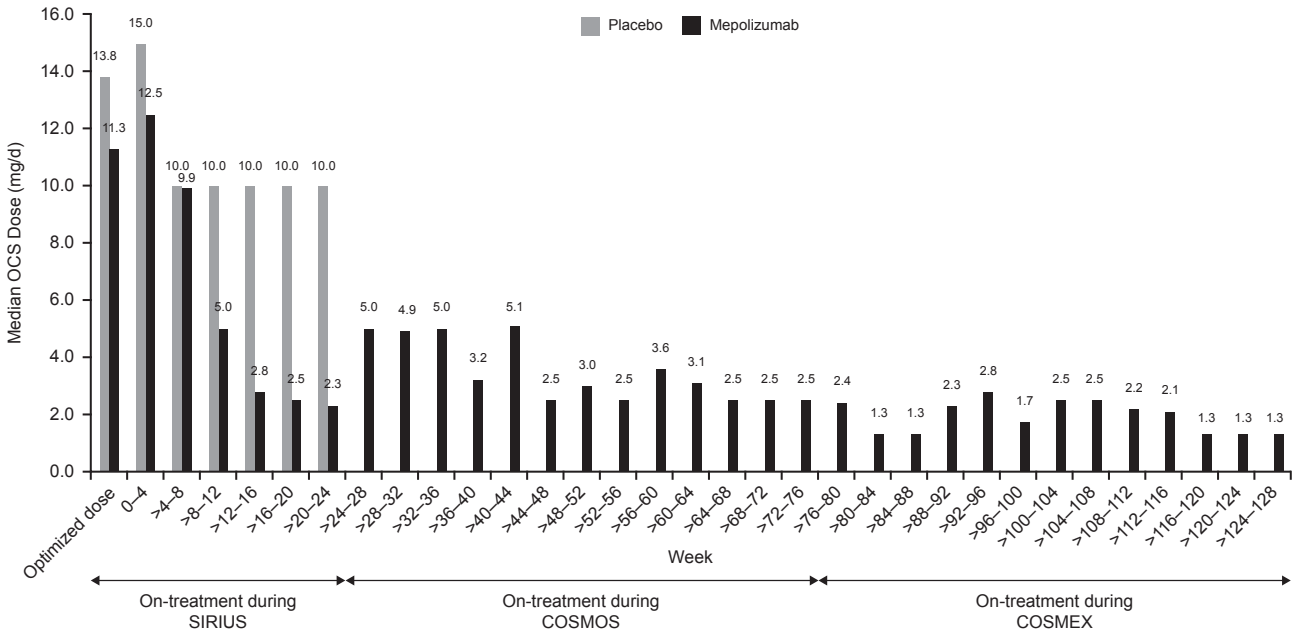


Figure 5. Oral corticosteroid (OCS) use throughout the SIRIUS (Steroid Reduction with Mepolizumab Study), COSMOS (A Study to Determine Long-term Safety of Mepolizumab in Asthmatic Subjects), and COSMEX (COSMOS Extension) studies in patients with ≥128 weeks of continuous enrollment. In total, 38 patients with ≥128 weeks of continuous reporting across SIRIUS, COSMOS, and COSMEX with ≤12 weeks between the last dose in COSMOS and first dose in COSMEX are summarized (SIRIUS, placebo, n = 18; mepolizumab, n = 20). Data are summarized in terms of prednisone equivalent dose.

and a loss of asthma control (according to the Juniper Asthma Control Questionnaire) over the 12-month follow-up period.[20] This scenario indicates that short-term use of mepolizumab (up to ~18 months) seemed to have no long-term disease-modifying effect in adult patients with severe asthma, and thus continuous treatment is necessary to obtain a sustained clinical benefit. It should be noted that despite these findings, and as observed in the COLUMBA study,[16] the interruption in treatment between COSMOS and COSMEX had no subsequent negative impact on the safety and efficacy of mepolizumab after treatment was resumed. Although a worsening in the interrupted group and further improvements in the continuous group, respectively, were observed in FEV_1 and ACQ-5 scores toward the end of the study, these findings were most likely a reflection of the low patient numbers at later time points.

The current study has several limitations. Regarding the study design, the lack of a placebo-controlled arm means it is difficult to make robust clinical interpretations regarding any treatment-related outcomes. Patient recruitment to this extension study was also biased toward those who responded to mepolizumab, and those without AEs leading to discontinuation from the previous studies, which may have positively affected long-term mepolizumab safety and efficacy. Approximately 370 of the 651 patients from COSMOS were eligible for continued mepolizumab treatment within COSMEX when assessed against the life-threatening/seriously debilitating and clinical benefit eligibility criteria, with the majority (92%) of eligible patients entering this extension study. Subsequently, the percentage of patients enrolled into COSMEX from the COSMOS trial was ~50%, and into COSMOS from the MENSA and SIRIUS trials was ~90%. These proportions are noteworthy because, owing to the nature of the studies, each subsequent study favored patients who responded to mepolizumab; however, these criteria for continued treatment are consistent with those of clinical practice. The use of background asthma therapies was also not systematically checked during this study; instead, it was at the investigator's discretion whether to reduce or change background therapies. This approach may have influenced the results to some extent, and in particular, any changes in bronchodilator therapy may have affected the results on lung function. Owing to the attrition of patients during this study, later-stage efficacy endpoints should also be interpreted with caution because the results are based on fewer patients compared with the first 2 years of the COSMEX study.

CONCLUSIONS

The long-term safety profile of mepolizumab 100 mg SC every 4 weeks in patients with the most severe forms of severe eosinophilic asthma and responsive to mepolizumab was similar to that seen in previous mepolizumab studies in patients with severe eosinophilic asthma, with no new safety concerns identified. In this selected group of patients, improvements in asthma control and reductions in blood eosinophil levels were maintained, and a strong and consistent reduction in exacerbations and chronic OCS use was sustained over time with prolonged mepolizumab treatment, whereas cessation of mepolizumab treatment led to loss of asthma control. Together, these findings confirm the stable and persistent response to mepolizumab observed in previous clinical trials and support the use of mepolizumab as a long-term treatment choice for patients with severe eosinophilic asthma.

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Dr. Albers, Dr. Bradford, Mr Gilson, and Mr Price were involved in the conception or design of the work; Dr. Khurana, Prof. Brusselle, Prof. Bel, Dr. FitzGerald, Dr. Masoli, Dr. Korn, Prof. Humbert, and Dr. Kato were involved in the acquisition of data; and all authors participated in data analysis and interpretation of the work. All authors critically revised the manuscript for intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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

DISCLOSURES

Dr. Khurana reports grants from GlaxoSmithKline (GSK) and Sanofi. Prof. Brusselle reports honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer, Teva and Zambon; and is a member of advisory boards for AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Sanofi/Regeneron, and Teva. Prof. Bel reports grants from AstraZeneca, GSK, and Novartis; and personal fees from AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Sanofi/Regeneron, Teva, and Vectura. Dr. FitzGerald reports personal fees from AstraZeneca, Boehringer Ingelheim, GSK, Merck, Novartis, Pfizer, Sanofi/Regeneron, and Teva; and grants from Amgen, AstraZeneca, GSK, Johnson & Johnson, and Sanofi/Novartis. Dr. Masoli reports grants from AstraZeneca, GSK, and Novartis; and personal fees from AstraZeneca and Novartis. Dr. Korn reports honoraria and grants from AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Sanofi, and Teva. Dr. Albers was an employee of GSK at the time this work was carried out, and holds stocks/shares in GSK. Dr. Bradford, Mr Gilson, and Mr Price are employees of GSK and hold stock/stock options in GSK. Prof. Humbert reports personal fees from AstraZeneca, Novartis, Roche, Sanofi and Teva; and grants and personal fees from GSK. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

GSK was responsible for the monitoring, analyses, and reporting of this study, and provided protocol-specific training for all investigators and responsible study site staff. Study protocol procedures, study requirements, and Good Clinical Practice responsibilities were reviewed by GSK. GSK funded medical writing support for this article; however, the authors made the final decision to submit the article for publication.

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APPENDIX A. SUPPLEMENTARY MATERIAL

The following are the supplementary data to this article:

Study Locations

The study was conducted in the following countries: Argentina, Australia, Belgium, Canada, Chile, Czechia, France, Germany, Italy, Japan, South Korea, the Netherlands, Poland, the Russian Federation, Spain, Ukraine, UK and USA.

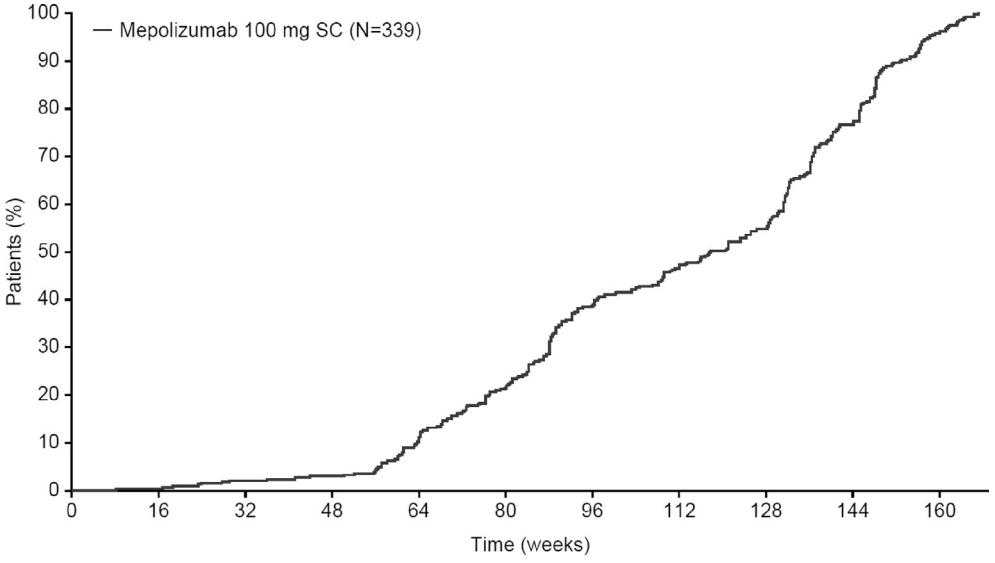
Protocol-defined Discontinuation Criteria

Each of the following constituted a protocol-defined discontinuation criterion: mepolizumab became commercially available in the relevant participating country; the sponsor discontinued the study in the relevant participating country; the patient was withdrawn by their physician; the patient withdrew consent; or the benefit/risk profile for the patient was no longer positive in the opinion of the investigator (supplementary Table I).

Protocol-defined Clinical Benefit

The protocol-defined clinical benefit inclusion criteria were dependent on the patient's previous study enrollment and the randomized treatment that they were assigned to within MENSA/SIRIUS.

- Patients from MENSA were required to have:
  - o A reduction in exacerbation frequency by $\geq$ 50% compared with the 12 months prior to screening for MENSA, during MENSA for those patients randomized to mepolizumab, and during the first 8 months of COSMOS for those randomized to placebo.
  - o Investigator-confirmed improvement during MENSA for those randomized to mepolizumab, and during COSMOS for those randomized to placebo.
- Patients from SIRIUS were required to have:
  - o A reduction in oral corticosteroids (OCS) dose by $\geq$ 50% compared with the patient's optimized OCS dose at randomization in SIRIUS, during SIRIUS for those randomised to mepolizumab, and during the first 6 months of COSMOS for those randomised to placebo.
  - o Investigator-confirmed improvement during SIRIUS for those randomised to mepolizumab, and during COSMOS for those randomised to placebo.



Supplementary Figure 1. Time to study cessation in COSMEX. Study closure was conducted in a staged manner as mepolizumab became commercially available for prescription in each participating country. SC = subcutaneous.

Supplementary Table I. Patient disposition and reasons for cessation from COSMEX.

	Mepolizumab 100 mg SC (N = 339)
Completion status, n (%)	
Discontinued	339 (100)
Completed	0 (0)
Reason for study cessation	
Mepolizumab commercially available[a]	159 (47)
Study closed/terminated	153 (45)
Withdrawal of consent	15 (4)
Lost to follow-up	4 (1)
Adverse event[b]	3 (0.9)
Lack of efficacy	2 (0.6)
Protocol deviation	2 (0.6)
Pregnancy	1 (0.3)
Prohibited medication use	1 (0.3)
Met protocol-defined liver chemistry stopping criteria[b]	1 (0.3)

[a] One patient withdrew from the study because mepolizumab became commercially available and died after receiving a single commercially available dose.
[b] Elevated liver chemistry results also considered an adverse event. SC = subcutaneous.

Supplementary Table II. Oral corticosteroid use throughout the SIRIUS, COSMOS and COSMEX studies in patients with ≥232 weeks of continuous enrollment.

Patients with data up to 232 weeks (n = 14[a])	OCS dose, median, mg/day	
	Placebo	Mepolizumab 100 mg SC
SIRIUS		
Optimized dose	10.0	12.5
Weeks 0–4	10.0	12.5
Weeks 4–8	6.7	10.0
Weeks 8–12	10.0	5.0
Weeks 12–16	9.0	5.0
Weeks 16–20	5.0	2.5
Weeks 20–24	2.5	2.2
COSMOS		
Weeks 24–28	–	1.7
Weeks 28–32	–	1.6
Weeks 32–36	–	1.4
Weeks 36–40	–	2.6
Weeks 40–44	–	2.9
Weeks 44–48	–	1.9
Weeks 48–52	–	1.9
Weeks 52–56	–	1.9
Weeks 56–60	–	3.0
Weeks 60–64	–	1.9
Weeks 64–68	–	3.8
Weeks 68–72	–	3.8
Weeks 72–76	–	1.9
COSMEX		
Weeks 76–80	–	1.3
Weeks 80–84	–	1.3
Weeks 84–88	–	1.3
Weeks 88–92	–	1.5
Weeks 92–96	–	1.3
Weeks 96–100	–	1.3
Weeks 100–104	–	1.6
Weeks 104–108	–	2.5
Weeks 108–112	–	1.9
Weeks 112–116	–	1.9
Weeks 116–120	–	0.6
Weeks 120–124	–	0.6
Weeks 124–128	–	1.3

Exclusion Criteria

Exclusion criteria included: a clinically significant change in health status during the COSMOS study, according to the investigator; pregnancy or breastfeeding; current smokers; or a clinically significant electrocardiogram abnormality determined by the investigator. Patients who received placebo in MENSA and had no exacerbations during that study and patients who received placebo in SIRIUS and were able to discontinue OCS therapy by the end of the study were not deemed severe enough to continue to receive mepolizumab in the COSMEX study.

- Screen failure: 1 patient was excluded due to a screening failure; they did not meet inclusion/exclusion for exacerbation history (i.e. received

Supplementary Table II. (*Continued*)

Patients with data up to 232 weeks (n = 14[a])	OCS dose, median, mg/day	
	Placebo	Mepolizumab 100 mg SC
Weeks 128–132	–	0.6
Weeks 132–136	–	0.6
Weeks 136–140	–	1.6
Weeks 140–144	–	1.4
Weeks 144–148	–	2.5
Weeks 148–152	–	1.9
Weeks 152–156	–	1.9
Weeks 156–160	–	0.0
Weeks 160–164	–	0.0
Weeks 164–168	–	1.0
Weeks 168–172	–	0.6
Weeks 172–176	–	0.6
Weeks 176–180	–	0.0
Weeks 180–184	–	0.0
Weeks 184–188	–	0.0
Weeks 188–192	–	0.0
Weeks 192–196	–	1.3
Weeks 196–200	–	2.1
Weeks 200–204	–	1.3
Weeks 204–208	–	0.0
Weeks 208–212	–	0.0
Weeks 212–216	–	0.0
Weeks 216–220	–	0.0
Weeks 220–224	–	0.0
Weeks 224–228	–	0.0
Weeks 228–232	–	0.0

[a] In total, 14 patients had ≥232 weeks of continuous reporting across SIRIUS, COSMOS, and COSMEX with ≤12 weeks between the last dose in COSMOS and the first dose in COSMEX. Of these 14 patients, 7 and 7 received placebo and mepolizumab, respectively, during the double-blinded SIRIUS study and then received mepolizumab during the open-label COSMOS and COSMEX studies. Data are summarized in terms of prednisone equivalent dose. OCS = oral corticosteroid; SC = subcutaneous.

Supplementary Table III. Number of patients achieving a total reduction in oral corticosteroid use throughout the SIRIUS, COSMOS and COSMEX studies in patients with ≥232 weeks of continuous enrollment.

Patients with data up to 232 weeks (n = 14[a])	n/N (%) with 100% reduction in OCS dose	
	Placebo	Mepolizumab 100 mg SC
SIRIUS		
Optimized dose	0	0
Weeks 0–4	0	0
Weeks 4–8	0	0
Weeks 8–12	0	0
Weeks 12–16	0	0
Weeks 16–20	0	1/7 (14%)
Weeks 20–24	2/7 (29%)	1/7 (14%)
COSMOS		
Weeks 24–28	–	2/13 (15%)
Weeks 28–32	–	2/13 (15%)
Weeks 32–36	–	2/14 (14%)
Weeks 36–40	–	3/14 (21%)
Weeks 40–44	–	4/14 (29%)
Weeks 44–48	–	4/14 (29%)
Weeks 48–52	–	4/14 (29%)
Weeks 52–56	–	4/14 (29%)
Weeks 56–60	–	4/14 (29%)
Weeks 60–64	–	4/14 (29%)
Weeks 64–68	–	3/14 (21%)
Weeks 68–72	–	3/14 (21%)
Weeks 72–76	–	4/14 (29%)
COSMEX		
Weeks 76–80	–	3/13 (23%)
Weeks 80–84	–	5/13 (38%)
Weeks 84–88	–	6/14 (43%)
Weeks 88–92	–	5/14 (36%)
Weeks 92–96	–	5/14 (36%)
Weeks 96–100	–	5/14 (36%)
Weeks 100–104	–	5/14 (36%)
Weeks 104–108	–	3/13 (23%)

(*continued on next page*)

Supplementary Table III. (*Continued*)

Patients with data up to 232 weeks (n = 14[a])	n/N (%) with 100% reduction in OCS dose	
	Placebo	Mepolizumab 100 mg SC
Weeks 108–112	–	4/13 (31%)
Weeks 112–116	–	4/13 (31%)
Weeks 116–120	–	7/14 (50%)
Weeks 120–124	–	7/14 (50%)
Weeks 124–128	–	6/14 (43%)
Weeks 128–132	–	7/14 (50%)
Weeks 132–136	–	7/14 (50%)
Weeks 136–140	–	5/14 (36%)
Weeks 140–144	–	3/12 (25%)
Weeks 144–148	–	3/12 (25%)
Weeks 148–152	–	5/14 (36%)
Weeks 152–156	–	5/14 (36%)
Weeks 156–160	–	8/14 (57%)
Weeks 160–164	–	8/14 (57%)
Weeks 164–168	–	6/14 (43%)
Weeks 168–172	–	7/14 (50%)
Weeks 172–176	–	7/14 (50%)
Weeks 176–180	–	9/14 (64%)
Weeks 180–184	–	8/13 (62%)
Weeks 184–188	–	8/13 (62%)
Weeks 188–192	–	8/14 (57%)
Weeks 192–196	–	6/13 (46%)
Weeks 196–200	–	4/14 (29%)
Weeks 200–204	–	7/14 (50%)
Weeks 204–208	–	8/14 (57%)
Weeks 208–212	–	9/14 (64%)
Weeks 212–216	–	9/14 (64%)
Weeks 216–220	–	8/13 (62%)
Weeks 220–224	–	8/13 (62%)
Weeks 224–228	–	7/12 (58%)
Weeks 228–232	–	7/12 (58%)

[a] In total, 14 patients had ≥232 weeks of continuous reporting across SIRIUS, COSMOS and COSMEX with ≤12 weeks between the last dose in COSMOS and the first dose in COSMEX. Of these 14 patients, 7 and 7 received placebo and mepolizumab, respectively, during the double-blinded SIRIUS study and then received mepolizumab during the open-label COSMOS and COSMEX studies. Data are summarized in terms of prednisone equivalent dose. OCS = oral corticosteroid; SC = subcutaneous.

placebo in MENSA but had no exacerbations during the study).

Adverse Events (AEs) of Special Interest

Within the mepolizumab clinical development program, AEs of special interest 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.

AEs Leading To Patient Withdrawal From Trial

Further details of the four patients who withdrew from COSMEX due to AEs are provided below:

- A 25-year-old male was withdrawn due to AEs of asthma exacerbation, anxiety disorder and neurodermatitis, each noted as severe.
- A 53-year-old male was withdrawn due to an AE of elevated liver function test, noted as severe. This was noted by the investigator as being related to health supplements (silymarin and saw palmetto).
- A 53-year-old female was withdrawn due to an AE of musculoskeletal pain, noted as severe, and considered related to treatment by the reporting investigator.
- A 65-year-old female experienced an on-treatment serious AE of severe asthma exacerbation and was withdrawn from the study; this patient subsequently developed multiple organ dysfunction and systemic inflammatory response syndrome post-treatment, both of which were fatal, as described below.

Fatalities In COSMEX

Further details of the two deaths occurring in COSMEX, both of which were not considered related to study treatment by the investigator, are provided below:

- A 65-year-old female died of severe asthma exacerbation, leading to multiple organ dysfunction and systemic inflammatory response syndrome.
- A 72-year-old female with a history of aortic valve stenosis died of brain hypoxia, cardio-respiratory arrest, and cerebrovascular disorder. Her death occurred after she withdrew from the study, because of mepolizumab becoming commercially available, and after taking the first dose of commercially available mepolizumab.