

Long-Term Efficacy and Safety of Mepolizumab in Patients With Severe Eosinophilic Asthma: A Multi-Center, Open-Label, Phase IIIb Study

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ABSTRACT

Purpose: Patients with severe eosinophilic asthma often experience recurrent asthma exacerbations despite intensive inhaled corticosteroid therapy. In 2 previous double-blind studies (MENSA [NCT01691521] and SIRIUS [NCT01691508]), treatment with intravenous or subcutaneous mepolizumab was associated with significantly reduced annualized exacerbation rates and oral corticosteroid (OCS) requirements compared with placebo. The purpose of this study was to assess the long-term safety and efficacy of subcutaneous mepolizumab treatment in patients with severe eosinophilic asthma.

Methods: COSMOS was a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or SIRIUS. Patients received subcutaneous mepolizumab regardless of prior treatment allocation and continued to receive appropriate standard-of-care asthma therapy throughout. The primary objective was to assess the long-term safety of mepolizumab; end points included adverse events (AEs) and serious AEs (SAEs). Efficacy assessments included the annualized exacerbation rate and durability of response (defined as the exacerbation rate and OCS

dose reduction when combined with MENSA and SIRIUS data, respectively).

Findings: In total, 558 (86%; previous mepolizumab: 358; previous placebo: 200) and 94 (14%; previous mepolizumab: 58, previous placebo: 36) patients experienced on-treatment AEs and SAEs, respectively. No fatal AEs were reported. Totals of 13 (2%) and 29 (4%) patients experienced systemic and local site reactions, respectively. There were no reports of mepolizumab-related anaphylaxis. Mepolizumab treatment was shown to exert a durable response, with patients who previously received mepolizumab in MENSA or SIRIUS maintaining reductions in exacerbation rate and OCS dosing throughout COSMOS. Patients who previously received placebo in MENSA or SIRIUS demonstrated improvements in these end points following treatment with mepolizumab in COSMOS.

Implications: These data demonstrate a favorable safety profile of mepolizumab and indicate a durable and stable effect over time, supporting long-term treatment in patients with severe eosinophilic asthma.

Accepted for publication July 20, 2016.

<http://dx.doi.org/10.1016/j.clinthera.2016.07.010>
0149-2918/\$ - see front matter

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ClinicalTrials.gov identifier: NCT01842607. (*Clin Ther.* 2016;■:■■■-■■■) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: durability, exacerbations, mepolizumab, severe eosinophilic asthma, safety.

INTRODUCTION

Severe asthma is a heterogeneous condition including several clinical phenotypes that differ in severity and response to therapy.^{1,2} One such phenotype is severe eosinophilic asthma, which is characterized by eosinophilic airway inflammation.^{1,2} These patients often experience recurrent asthma exacerbations despite intensive asthma therapy with high-dose inhaled corticosteroids or oral corticosteroids (OCSs) plus controllers,³ leading to increased morbidity and mortality.^{4,5}

Mepolizumab is a humanized anti-interleukin-5 monoclonal antibody that was recently approved in several countries/regions, including Australia, Japan, Canada, Europe, and the United States, for the treatment of severe eosinophilic asthma in adults. The efficacy of mepolizumab in this patient population has been demonstrated in 3 randomized, controlled clinical trials, SIRIUS (Steroid Reduction with Mepolizumab Study), MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma), and DREAM (Dose Ranging Efficacy and Safety with Mepolizumab).⁶⁻⁸

The 52-week, double-blind, placebo-controlled DREAM study (ClinicalTrials.gov identifier: NCT 01000506) assessed asthma exacerbation rates in patients with severe eosinophilic asthma receiving 1 of 3 doses of intravenous mepolizumab or placebo; there were significant reductions in the rate of asthma exacerbations of 39% to 52% across all intravenous mepolizumab treatment groups compared with placebo.⁸ In the pivotal 32-week, double-blind MENSA study (ClinicalTrials.gov identifier: NCT01691521), treatment with intravenous or subcutaneous mepolizumab within this patient population was associated with significant reductions in annualized exacerbations, by 47% and 53%, respectively, compared with placebo.⁷ Furthermore, in the 24-week, double-blind, placebo-controlled SIRIUS study (ClinicalTrials.gov identifier: NCT01691508), subcutaneous mepolizumab was associated with a reduced need for treatment with OCSs,

reduced annualized exacerbation rates, and improved asthma control.⁶ This reduction in OCS use is of importance because treatment with OCSs has a considerable impact on patients' lives owing to the associated corticosteroid-related adverse effects.⁹⁻¹¹ While all 3 studies reported the prevalence of adverse events (AEs) and assessed basic safety variables, the long-term safety and durability of the response to subcutaneous mepolizumab in patients with severe eosinophilic asthma are not fully established.

This article describes COSMOS, the first completed, dedicated long-term safety study (a 52-week, open-label extension of the MENSA and SIRIUS studies) of subcutaneous mepolizumab, conducted in patients with severe eosinophilic asthma. In addition, the durability and stability of the response to treatment with subcutaneous mepolizumab were assessed in terms of reductions in exacerbations and OCS dose.

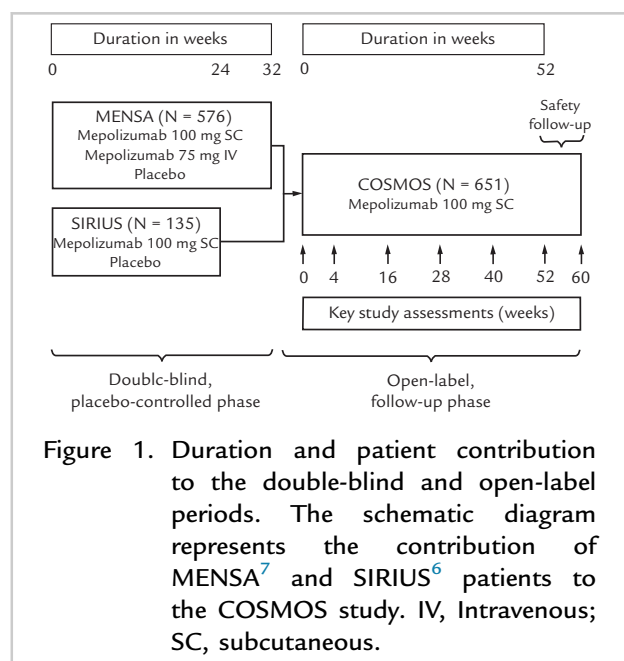
PATIENTS AND METHODS

Study Design

COSMOS was a 52-week, multicenter, open-label, Phase IIIb study that assessed the safety of mepolizumab 100 mg SC in patients with severe eosinophilic asthma. The study was conducted between May 2013 and March 2015, at 139 centers across 19 countries. The study was performed in accordance with the Good Clinical Practice guidelines, the ethics principles outlined in the Declaration of Helsinki 2008, and in accordance with institutional review board approvals/processes.

Patients completing the MENSA or SIRIUS study (both reported separately)^{6,7} were given the opportunity to provide consent for participation in this open-label extension study in which all participants received mepolizumab regardless of treatment allocation in those 2 double-blind studies. The last visit in either previous study served as the baseline visit for the present study (Figure 1).

In COSMOS, mepolizumab 100 mg SC was administered at baseline (visit 1; week 0), and then every 4 weeks for a total of 48 weeks, as an add-on to appropriate standard of care that could be adjusted at the physician's discretion. Fourteen visits were completed to week 52, with a follow-up visit 12 weeks after each patient's last dose.



Patients

Eligible patients were ≥ 12 years of age, had completed the MENSA or SIRIUS study,^{6,7} and were being treated with an inhaled corticosteroid and another asthma controller medication throughout either study. Patients were expected to continue on controller therapy throughout the duration of this study. All patients provided written informed consent prior to the performance of any study-specific procedures.

Female patients of childbearing potential were required to commit to consistent and correct use of acceptable birth control methods for the duration of the study, and for 4 months after the last administration of study drug; pregnancy testing was performed in all female patients prior to enrollment, during each scheduled study visit prior to administration of study drug, and during the follow-up visit. Patients in France were eligible for inclusion only if they were affiliated with, or a beneficiary of, a social security category.

Exclusion criteria included the following occurrences during the MENSA or SIRIUS study: a study medication-related hypersensitivity reaction that led to withdrawal; a clinically significant change in health status that the investigator thought might make the patient unsuitable for participation in this study; a malignancy; a serious AE (SAE) judged by the investigator as possibly related to study medication; an

alanine or aspartate aminotransferase, or alkaline phosphatase, level ≥ 2 -fold the upper limit of normal; and/or a bilirubin level ≥ 1.5 -fold the upper limit of normal. Other exclusion criteria included pregnancy; baseline ECG values indicative of a clinically significant abnormality; being a current smoker; and/or a positive hepatitis B surface antigen result at visit 1. The use of other monoclonal antibodies, including omalizumab, as well as other investigational drugs and experimental anti-inflammatory drugs (nonbiologics) was prohibited.

Procedures

Patient Assessments

Demographic information and medical history, including asthma therapy history, were assessed at baseline (visit 1; week 0). Concurrent medications (including OCS dose) were assessed at every clinic visit.

Safety Assessments

The occurrences of AEs and SAEs, including cardiovascular (CV) events (adjudicated by a clinical end point committee), investigator-defined systemic allergic and nonallergic reactions, and local site reactions were reported at all visits. The following prespecified events were adjudicated by the clinical end point committee: cerebrovascular events, including stroke and transient ischemic attack; congestive heart failure; deep vein thrombosis; myocardial infarction/unstable angina; peripheral arterial thromboembolism; and all-cause death. All systemic reactions were assessed for anaphylaxis using the diagnostic criteria defined by Sampson et al.¹² Twelve-lead ECGs were assessed at baseline and at weeks 28, 52 (exit visit), and 60 (or 12 weeks following last dose; follow-up visit). Vital signs were assessed at all visits, and clinical laboratory variables were assessed at various time points.

Efficacy Assessments

Assessment for exacerbations occurred at every clinic visit. The 5-item Asthma Control Questionnaire (ACQ-5) score (scale: 0 = totally controlled, to 6 = severely uncontrolled) was assessed at baseline and at weeks 4, 16, 28, 40, 52 (exit visit), and 60 (or 12 weeks following last dose; follow-up). Forced expiratory volume in 1 second (FEV₁) was assessed at baseline and at weeks 16, 28, and 52 (exit visit).

Blood eosinophil count was assessed at baseline and at weeks 4, 16, 28, 52, and 60 (or 12 weeks following last dose; follow-up).

Immunogenicity Assessments

Immunogenicity testing included 2 assays: (1) a binding antibody assay for antidrug antibody (ADA); and (2) a neutralizing antibody assay in patients who tested positive on the ADA assay. These assessments were conducted at baseline and at weeks 52 (exit visit) and 60 (or 12 weeks following last dose; follow-up).

Study Objectives

The primary objective of the study was to describe the long-term safety profile of mepolizumab in patients with severe eosinophilic asthma. The secondary objective was to evaluate the efficacy of long-term mepolizumab treatment in terms of a range of clinical markers of asthma control, including the annualized rate of exacerbations, ACQ-5 score, and FEV₁. Durability of response, defined as the rate of exacerbations and OCS dose, was also assessed; however, this end point was not prespecified in the protocol and was assessed post hoc.

Statistical Analysis

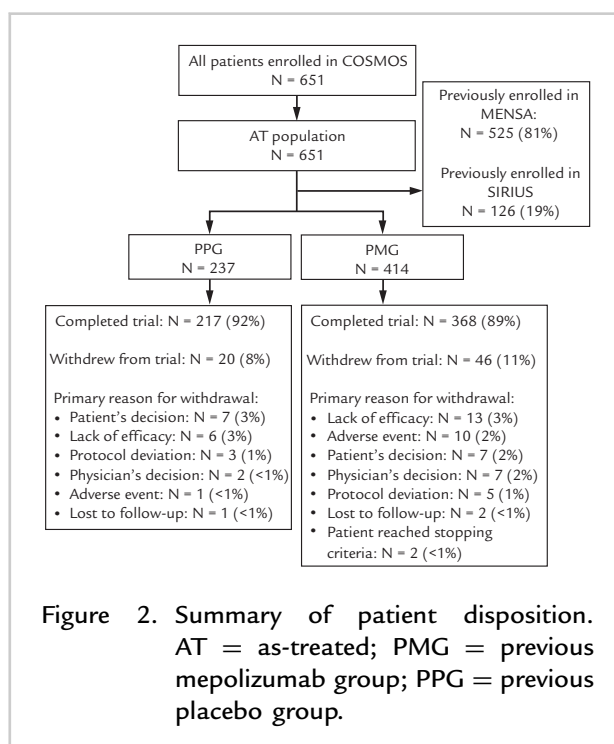
No sample size was calculated; the study population was determined by the number of patients randomized into the MENSA or SIRIUS study who were eligible for COSMOS. The as-treated population, consisting of all patients who received at least 1 dose of open-label mepolizumab, was the population used for all analyses. Data are summarized using appropriate descriptive statistics (means/geometric means, SDs, medians, and ranges).

AEs were summarized using the Medical Dictionary for Regulatory Activities primary System Organ Class and preferred terms. The annualized rate of exacerbations was estimated using a negative binomial generalized linear model, with a log-link function,¹³ from which the estimated rate per year and associated 95% CI were calculated. Time to first exacerbation was summarized using Kaplan–Meier estimates. ACQ-5 score and FEV₁ were assessed as changes from baseline. For blood eosinophil counts, values below the lower limit of quantification were imputed with half of the lower limit of quantification prior to log-transformation. Post hoc analysis of durability of response was conducted by combining the data

from this open-label study (COSMOS) with those from the previous double-blind studies (MENSA and SIRIUS^{6,7}) in patients who completed 2 studies. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

In total, 651 patients were enrolled into COSMOS (525 [91%] and 126 [93%] of those randomized in MENSA and SIRIUS, respectively^{6,7} and were included in the as-treated population. Of these, 414 patients (64%) had previously received mepolizumab intravenously or subcutaneously in MENSA or SIRIUS (previous mepolizumab group [PMG]), and 237 (36%) had previously received placebo (previous placebo group [PPG]) in MENSA or SIRIUS (and therefore received mepolizumab for the first time at visit 1 of COSMOS). Sixty-six patients (10%) were withdrawn from the study. The most common reasons for withdrawal were a lack of efficacy (19 patients [3%]), patient's decision (14 patients [2%]), AEs (11 patients [2%]), physician's decision (9 patients [1%]), and protocol deviation patients (8 [1%], which included 4 patients [$<1\%$] who became pregnant and 3 patients [$<1\%$] due to lack of adherence). Baseline



characteristics were generally comparable between patients who withdrew and the total patient population, although the mean baseline ACQ-5 score and prebronchodilator FEV₁ value were slightly worse in those who withdrew. Patient disposition is summarized in [Figure 2](#).

Overall, patients' demographic and clinical characteristics at COSMOS baseline were well-balanced between previous treatment groups ([Table I](#)). Differences in ACQ-5 scores, lung function, and blood eosinophil counts between the PPG and PMG reflected the treatments originally received during MENSA and SIRIUS (ie, mepolizumab or placebo).

By the end of COSMOS, a total of 691 patients had received mepolizumab treatment in MENSA, SIRIUS, or COSMOS. Of these, 614 (89%) and 362 (52%) patients had received continuous mepolizumab treatment for at least 12 and 18 months, respectively. The median cumulative exposure to mepolizumab was 17.6 months (range, 1–22 months).

For the primary outcome of long-term safety, AEs were reported in 562 patients (86%). The majority of these patients (558 [86%]) experienced on-treatment AEs. Across the whole study population, the on-treatment AEs most commonly reported were nasopharyngitis (196 patients [30%]), upper respiratory tract infection (101 [16%]), and worsening or exacerbation of asthma (90 [14%]). In total, 123 patients (19%) had AEs considered as related to the study treatment. Similar numbers of AEs were observed between patients who had previously received mepolizumab (PMG) and patients who had previously received placebo (PPG). Safety data are summarized in [Table II](#).

In the overall population, SAEs were reported in 105 patients (16%), with 94 patients (14%) reporting an SAE while on treatment ([Table II](#)). The most common on-treatment SAEs in all patients included worsening or exacerbation of asthma (38 patients [6%]), pneumonia (4 patients [$<1\%$]), and atrial fibrillation (3 patients [$<1\%$]) ([Table II](#)). Two patients ($<1\%$) experienced SAEs considered related to the study treatment (type IV hypersensitivity reaction in the PMG, which was resolved, and spontaneous abortion in the PPG). Similar numbers of SAEs were reported in the PMG and the PPG ([Table II](#)). No fatal SAEs were reported during the study. A total of 15 patients (2%) experienced CV events, of whom 3 patients ($<1\%$) experienced the

prespecified adjudicated CV events (stroke [PMG], deep vein thrombosis [PMG], and myocardial infarction requiring hospitalization [PPG]) as assessed by the clinical end point committee ([Table II](#)).

Systemic and local site reactions were reported in 13 (2%) and 29 (4%) patients, respectively. Slightly higher numbers of systemic reactions (7 [3%] vs 6 [1%]) and local site reactions (15 [6%] vs 14 [3%]) were observed in the PPG than in the PMG, respectively ([Table II](#)). There were no reports of anaphylaxis considered related to treatment with mepolizumab. The percentages of patients with abnormal ECG values throughout the study were similar between groups, with few clinically significant changes from baseline observed. Postbaseline vital sign and clinical laboratory measurements were generally similar to baseline values; few clinical chemistry values outside the normal range were observed at postbaseline visits.

During COSMOS, on-treatment asthma exacerbations were observed in 311 patients (48%) (rate per annum, 0.93), with 59 patients (9%) requiring hospitalization or an emergency department visit, and 39 (6%) requiring hospitalization only ([Table III](#)). The probability of experiencing at least 1 exacerbation increased throughout the treatment period, from 24.2% (95% CI, 21.0%–27.7%) at week 16, to 49.1% (95% CI, 45.2%–53.1%) at week 52 (see [Figure E1](#) and [Table E1](#) in the online version at doi:10.1016/j.clinthera.2016.07.010). All exacerbation data were similar between the PMG and the PPG ([Table III](#)) (see [Figure E1](#) and [Table E1](#) in the online version at doi:10.1016/j.clinthera.2016.07.010 and were consistent with those from the double-blind studies).

For ACQ-5 and FEV₁, the improvements from baseline observed in the PMG during previous double-blind treatment were maintained through week 52 of the open-label period ([Table III](#)). In the PPG, for both outcomes, improvements were observed at the first postbaseline assessment and were maintained through week 52 ([Table III](#)). Following the discontinuation of mepolizumab treatment (last dose at week 48), higher ACQ-5 scores were reported at week 60 (follow-up) in both the PMG and PPG, indicating reduced asthma control compared with that at week 52.

Blood eosinophil count reductions demonstrated in the PMG during double-blind treatment were maintained throughout the open-label study ([Table III](#)). In

Table I. Patients' demographic and clinical characteristics at baseline (as-treated population).^{*} Data are given as number (%) of patients unless otherwise noted.

Characteristic	PPG (n = 237)	PMG (n = 414)	All Patients (n = 651)
Age, mean (SD), y	50.4 (13.4)	51.6 (14.1)	51.1 (13.9)
Female	125 (53)	235 (57)	360 (55)
Race			
White	192 (81)	338 (82)	530 (81)
Asian	38 (16)	61 (15)	99 (15)
Other	7 (3)	15 (4)	22 (3)
Non-Hispanic/Latino ethnicity	220 (93)	381 (92)	601 (92)
Body mass index	n = 236	n = 411	n = 647
Mean (SD), kg/m ²	28.2 (5.7)	27.9 (5.9)	28.0 (5.8)
Duration of asthma, mean (SD), y	20.1 (14.7)	20.3 (13.4)	20.2 (13.9)
Allergic rhinitis or hay fever	116 (49)	195 (47)	311 (48)
ACQ-5 score [†]	n = 220	n = 390	n = 610
Mean (SD)	1.76 (1.13)	1.25 (1.10)	1.44 (1.14)
Median (min, max)	1.60 (0.0, 5.2)	1.00 (0.0, 6.0)	1.20 (0.0, 6.0)
Prebronchodilator baseline FEV ₁ , mL	n = 237	n = 412	n = 649
Mean (SD)	1957 (668)	2010 (733)	1991 (710)
Median (min, max)	1880 (450, 4650)	1920 (480, 4780)	1910 (450, 4780)
Prebronchodilator FEV ₁ /FVC ratio	n = 237	n = 412	n = 649
Mean (SD)	0.64 (0.12)	0.66 (0.12)	0.65 (0.12)
Median (min, max)	0.64 (0.3, 0.9)	0.67 (0.3, 1.0)	0.66 (0.3, 1.0)
Reversibility of FEV ₁	n = 217	n = 379	n = 596
Mean (SD), %	17.2 (18.9)	15.9 (17.2)	16.4 (17.9)
Concurrent therapy			
ICS	237 (100)	409 (99)	646 (>99)
LABA	231 (97)	406 (98)	637 (98)
LTRA	111 (47)	184 (44)	295 (45)
Xanthine	49 (21)	79 (19)	128 (20)
LAMA	30 (13)	66 (16)	96 (15)
Blood eosinophil count, cells/μL	n = 230	n = 400	n = 630
Geometric mean (SD logs)	280 (0.926)	50 (0.914)	90 (1.248)
Median (min, max)	320 (10, 1900)	50 (10, 900)	80 (10, 1900)

ACQ-5 = 5-item Asthma Control Questionnaire; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroid; min = minimum; max = maximum; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor agonist; PMG = previous mepolizumab group; PPG = previous placebo group.

^{*}Table presents patients' characteristics when they commenced COSMOS.

[†]Scale scores: 0 = totally controlled, to 6 = severely uncontrolled.

the PPG, blood eosinophil counts (geometric mean [SD log]) were reduced from 280 (0.926) cells/μL at baseline (Table I) to 60 (0.886) cells/μL at week 4. A similar blood eosinophil count was maintained through week 52 (Table III). Following the discontinuation of

mepolizumab treatment (last dose at week 48), blood eosinophil counts increased to 160 (1.117) and 160 (1.141) cells/μL in the PPG and PMG populations, respectively, at week 60 (follow-up). The antihistamines ketotifen fumarate and rupatadine,

Table II. Summary of adverse events (AEs), including cardiovascular (CV) events and systemic and local reactions (as-treated population). Data are given as number (%) of patients unless otherwise noted.

Parameter	PPG (n = 237)	PMG (n = 414)	All Patients (N = 651)
Any AE*	202 (85)	360 (87)	562 (86)
On-treatment	200 (84)	358 (86)	558 (86)
Most common (occurring in $\geq 10\%$ of patients)			
Nasopharyngitis	82 (35)	114 (28)	196 (30)
Upper respiratory tract infection	40 (17)	61 (15)	101 (16)
Asthma†	36 (15)	54 (13)	90 (14)
Bronchitis	34 (14)	46 (11)	80 (12)
Headache	28 (12)	60 (14)	88 (14)
Sinusitis	23 (10)	43 (10)	66 (10)
Related to study treatment	48 (20)	75 (18)	123 (19)
Any SAE	41 (17)	64 (15)	105 (16)
On-treatment	36 (15)	58 (14)	94 (14)
Related to study treatment‡	1 (<1)	1 (<1)	2 (<1)
Most common (occurring in ≥ 2 patients)			
Asthma†	16 (7)	22 (5)	38 (6)
Atrial fibrillation	3 (1)	0	3 (<1)
Pneumonia	2 (<1)	2 (<1)	4 (<1)
Bronchitis	2 (<1)	0	2 (<1)
Appendicitis	1 (<1)	1 (<1)	2 (<1)
Upper respiratory tract infection	1 (<1)	1 (<1)	2 (<1)
Diverticulitis	0	2 (<1)	2 (<1)
Any fatal SAE	0	0	0
Any CV event	6 (3)	9 (2)	15 (2)
Any prespecified adjudicated CV event‡	1 (<1)	2 (<1)	3 (<1)
Myocardial infarction requiring hospitalization	1 (<1)	0	1 (<1)
Deep vein thrombosis	0	1 (<1)	1 (<1)
Stroke	0	1 (<1)	1 (<1)
Any systemic reaction	7 (3)	6 (1)	13 (2)
Any injection-related reaction (nonallergic)	5 (2)	2 (<1)	7 (1)
Hypersensitivity	1 (<1)	3 (<1)	4 (<1)
Type IV hypersensitivity	1 (<1)	2 (<1)	3 (<1)
Local injection-site reaction	15 (6)	14 (3)	29 (4)

PMG = previous mepolizumab group; PPG = previous placebo group; SAE = serious adverse event.

*Listed according to Medical Dictionary for Regulatory Activities terminology; other terms may be used.

†Asthma reported as an AE means worsening or exacerbation of asthma.

‡As assessed by the clinical end point committee.

§The following: SAEs related to treatment (investigator assessment) included Type IV hypersensitivity (PMG) and spontaneous abortion (PPG).

which have modest anti-eosinophilic properties, were taken by a small number of patients during the study. Ketotifen fumarate was taken during

treatment by 4 patients in the PPG group and 1 in the PMG group. Rupatadine or rupatadine fumarate was taken during treatment by 8 patients (4 in each group).

Table III. Summary of efficacy data (as-treated population).

Parameter	PPG (n = 237)	PMG (n = 414)	All Patients (N = 651)
On-treatment exacerbations*			
All exacerbations			
Patients, no. (%)	120 (51)	191 (46)	311 (48)
Exacerbations	246	408	654
Exacerbation rate per annum (95% CI)	0.99 (0.83–1.18)	0.90 (0.78–1.04)	0.93 (0.83–1.04)
Exacerbations requiring hospitalization or ED visit			
Patients, no. (%)	26 (11)	33 (8)	59 (9)
Exacerbations	38	57	95
Exacerbations requiring hospitalization			
Patients, no. (%)	16 (7)	23 (6)	39 (6)
Exacerbations	25	40	65
ACQ-5 score, change from baseline ^{†,‡}			
Week 4	n = 218	n = 385	n = 603
Mean (SD)	-0.28 (0.88)	0.01 (0.75)	-0.09 (0.81)
Median (min, max)	-0.20 (-3.4, 2.6)	0.00 (-3.0, 3.6)	0.00 (-3.4, 3.6)
Week 16	n = 215	n = 377	n = 592
Mean (SD)	-0.46 (0.91)	0.09 (0.87)	-0.11 (0.92)
Median (min, max)	-0.40 (-3.6, 3.0)	0.00 (-2.6, 4.2)	0.00 (-3.6, 4.2)
Week 28	n = 212	n = 365	n = 577
Mean (SD)	-0.33 (1.10)	0.12 (0.94)	-0.05 (1.02)
Median (min, max)	-0.20 (-3.0, 3.6)	0.00 (-2.8, 4.6)	0.00 (-3.0, 4.6)
Week 40	n = 210	n = 354	n = 564
Mean (SD)	-0.30 (1.03)	0.03 (0.87)	-0.10 (0.95)
Median (min, max)	-0.20 (-3.8, 3.8)	0.00 (-3.4, 3.8)	0.00 (-3.8, 3.8)
Week 52 (4-weeks following last dose)	n = 206	n = 350	n = 556
Mean (SD)	-0.30 (1.00)	0.04 (0.96)	-0.09 (0.99)
Median (min, max)	-0.20 (-3.8, 2.6)	0.00 (-4.0, 4.0)	0.00 (-4.0, 4.0)
Week 60 (follow-up; 12 weeks following last dose) [§]	n = 142	n = 196	n = 338
Mean (SD)	0.05 (1.19)	0.31 (1.08)	0.20 (1.13)
Median (min, max)	0.00 (-2.8, 4.8)	0.10 (-3.0, 3.6)	0.00 (-3.0, 4.8)
Prebronchodilator FEV ₁ , change from baseline (mL) [†]			
Week 16	n = 232	n = 400	n = 632
Mean (SD)	155 (384)	15 (340)	67 (363)
Median (min, max)	110 (-970, 1870)	-5 (-1310, 1460)	30 (-1310, 1870)
Week 28	n = 229	n = 386	n = 615
Mean (SD)	115 (451)	12 (379)	50 (410)
Median (min, max)	89 (-1950, 2540)	5 (-1660, 1760)	30 (-1950, 2540)
Week 52 (4 weeks following last dose)	n = 223	n = 379	n = 602
Mean (SD)	100 (448)	-13 (374)	29 (406)
Median (min, max)	50 (-1210, 2460)	-10 (-1580, 1400)	20 (-1580, 2460)
Blood eosinophil count (cells/ μ L) [†]			
Week 4	n = 228	n = 399	n = 627
Geometric mean (SD logs)	60 (0.886)	50 (0.948)	50 (0.931)

(continued)

Table III. (continued).

Parameter	PPG (n = 237)	PMG (n = 414)	All Patients (N = 651)
Median (min, max)	70 (10, 1000)	50 (10, 1200)	60 (10, 1200)
Week 16	n = 216	n = 383	n = 599
Geometric mean (SD logs)	50 (0.904)	50 (0.864)	50 (0.878)
Median (min, max)	60 (10, 400)	60 (10, 1100)	60 (10, 1100)
Week 28	n = 224	n = 378	n = 602
Geometric mean (SD logs)	50 (0.871)	50 (0.941)	50 (0.915)
Median (min, max)	50 (10, 400)	50 (10, 700)	50 (10, 700)
Week 52 (4-weeks following last dose)	n = 217	n = 373	n = 590
Geometric mean (SD logs)	50 (0.979)	50 (0.909)	50 (0.934)
Median (min, max)	50 (10, 600)	50 (10, 900)	50 (10, 900)
Week 60 (follow-up; 12 weeks following last dose) [§]	n = 148	n = 200	n = 348
Geometric mean (SD logs)	160 (1.117)	160 (1.141)	160 (1.129)
Median (min, max)	170 (10, 1900)	180 (10, 1200)	180 (10, 1900)

ACQ-5 = Asthma Control Questionnaire-5; AE = adverse event; ED = emergency department; FEV₁ = forced expiratory volume in 1 second; max = maximum; min = minimum; PMG = previous mepolizumab group; PPG = previous placebo group.

*Analysis of exacerbation rate performed using a negative binomial model with covariates of region, exacerbations in the year prior to MENSA⁷ or SIRIUS⁶ (as an ordinal variable) and % predicted FEV₁ from the baseline of MENSA⁷ or SIRIUS,⁶ with logarithm of time on treatment as an offset variable.

†Baseline data on these end points are summarized in Table II.

‡A negative number represents improvement in asthma control.

§This time point was in the follow-up phase.

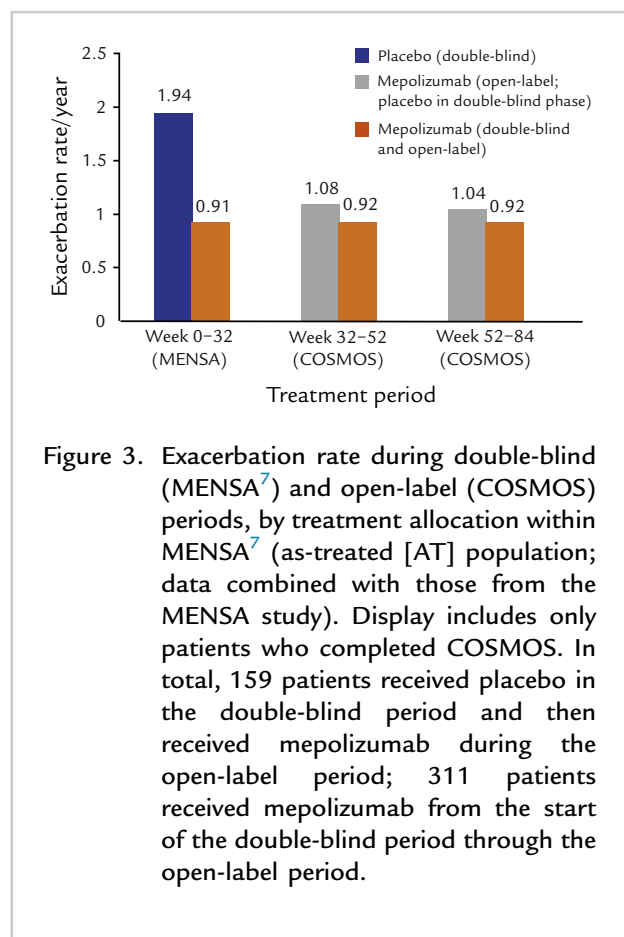
For the assessment of immunogenicity, within COSMOS, marginally more (20 patients [9%]) in the PPG had a positive ADA result postbaseline compared with those in the PMG (11 patients [3%]); positive ADA samples were infrequent, and the levels were generally low and transient. All of these patients were negative for neutralizing antibody.

In the post hoc analysis, treatment with mepolizumab exerted a durable response over the open-label period. In patients continuing to receive mepolizumab following the MENSA study, the exacerbation rate per year remained low across the double-blind and open-label treatment periods (Figure 3). In patients who received placebo in MENSA and mepolizumab in the open-label period, the exacerbation rate decreased after the switch to mepolizumab (Figure 3). On the assessment of median OCS dose, the reduction in median OCS dose achieved with mepolizumab during SIRIUS (10.0 mg/d at baseline to 2.5 mg/d at the end of SIRIUS) was maintained throughout the open-label period (Figure 4).

In patients who received placebo during SIRIUS, the median OCS dose was reduced from 12.3 mg/d at baseline to 10.0 mg/d at the end of SIRIUS; this rate was further reduced to 5.0 mg/d following 52 weeks of mepolizumab treatment within the open-label period (Figure 4). Additionally, in the group from SIRIUS, 16/58 patients (28%) in the PPG and 18/57 (32%) in the PMG were no longer receiving OCS treatment between weeks 48 and 52 (weeks 72–76 from SIRIUS baseline), compared with 6/61 (10%) and 13/65 (20%) patients when commencing COSMOS, respectively.

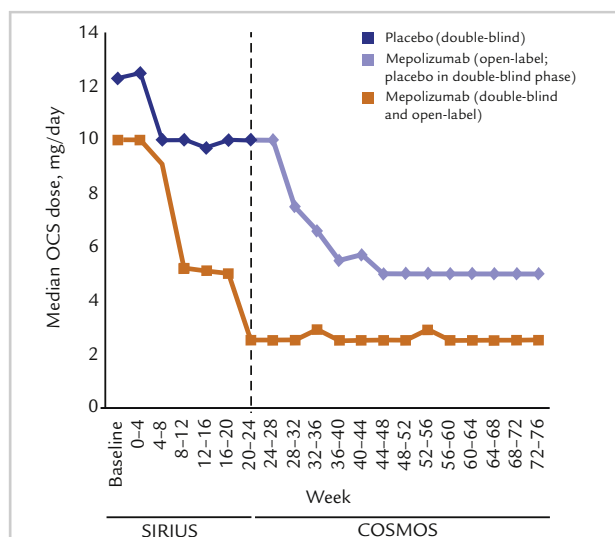
DISCUSSION

COSMOS was a dedicated long-term safety study of subcutaneous mepolizumab in patients with severe eosinophilic asthma. Overall, results showed a favorable long-term safety profile of subcutaneous mepolizumab that was consistent with those from previously published studies.^{6,7} There was a low prevalence of



on-treatment AEs and SAEs considered related to the study treatment ($\leq 20\%$ and $< 1\%$, respectively), and no reported mepolizumab-related anaphylactic reactions or fatal AEs. Very few CV events, systemic reactions, and local injection site reactions were reported.

The prevalence of AEs in the open-label extension compared favorably with those from the parent MENSA and SIRIUS studies.^{6,7} In MENSA and SIRIUS, the percentages of patients experiencing at least 1 AE were similar between the PPG and PMG groups, and these rates did not increase within this 52-week, open-label extension.^{6,7} Similarly, the rates of AEs related to treatment did not increase over this open-label extension compared with those from MENSA and SIRIUS. Since biologic drugs such as anti-interleukin-5 have the potential to invoke an immune reaction,¹⁴ it was reassuring that there were no cases of mepolizumab-related anaphylaxis, and that the overall frequency of systemic reactions



during the 52-week extension study was low (2%). The immunogenicity data collected were consistent with data from the DREAM, SIRIUS, and MENSA studies,⁶⁻⁸ which demonstrated that the majority of ADA-positive patients developed ADA within 16 weeks of the first dose and that positivity decreased over time.

Regarding efficacy, a low prevalence of exacerbations requiring hospitalization or an emergency department visit was observed with mepolizumab treatment, consistent with that observed with mepolizumab during the MENSA and SIRIUS randomized controlled studies.^{6,7} On-treatment exacerbation rates were also similar between patients in the PMG and the PPG. Mepolizumab treatment was shown to exert a durable efficacy response, with patients who previously received

mepolizumab in MENSA or SIRIUS maintaining improvements in the reductions in the exacerbation rates and OCS dosing throughout the open-label study.

One limitation of the SIRIUS study was the relatively short duration of exposure to mepolizumab during the double-blind period. A longer study would allow for the determination of whether more complete withdrawal of OCSs is possible and whether the outcomes are maintained over time. Nonetheless, COSMOS assessed OCS withdrawal in a limited number of patients from SIRIUS and found that an additional 5 and 10 patients in the PMG and PPG, respectively, were not receiving OCS treatment at the end compared with the start of COSMOS. Importantly, in COSMOS, clear improvements in exacerbation rates and OCS dosing were observed during open-label treatment in patients who previously received placebo. These data indicate that the treatment effects of mepolizumab are durable and stable over time.

It should be noted that the observed decreases in OCS dosing achieved during the open-label period were different from those observed in the SIRIUS study.⁶ These differences may have been due to the differences in the algorithms used to inform reductions in dosing in each study; in SIRIUS,⁶ the algorithm was protocol-driven (specified reductions in OCS dose on the basis of asthma control and symptoms of adrenal insufficiency),⁶ whereas in COSMOS, OCS reduction was dependent on each physician's judgment. Combined with the open-label study design, the OCS dose reduction observed during COSMOS may better reflect the results that may be achieved in clinical practice compared with those seen during SIRIUS. The decreases in daily OCS dose seen in COSMOS further support the benefits of mepolizumab treatment in providing a meaningful reduction in OCS dosing, with the possibility of reducing the side effects observed with long-term OCS treatment.^{10,11,15}

Prebronchodilator FEV₁ and ACQ-5 data in COSMOS indicated an improvement in patients in the PPG following the administration of mepolizumab treatment. The scale of these improvements was consistent with those observed in the MENSA and SIRIUS studies.^{6,7} No further improvement in FEV₁ or ACQ-5 was observed in the PMG. This observation suggests that the improvements achieved are evident early after the initiation of therapy and are stable over time, as per the durability-of-response end points discussed earlier. The interpretation of these long-term effects of

mepolizumab on prebronchodilator FEV₁, however, should be made in the context of the expected decline in lung function in this patient population, which may vary between ~20 and 50 mL/y.^{16–18} Potential changes in treatment compliance should also be considered, as increased disease stability from treatment may lead to reduced treatment compliance with inhaled medications.

Suppression of the eosinophil response is a clinically relevant marker of efficacy in the population assessed during this study. A rapid, sustained reduction in blood eosinophils was observed in the PPG following mepolizumab treatment; this trend is consistent with those in the previous double-blind studies.^{6,7} This finding, together with the sustained reduction in blood eosinophil count in the PMG, suggests that the suppressive effect of mepolizumab on interleukin-5 translates into a beneficial effect in this patient population, supported by the observed benefits on markers of asthma control. Of note, after patients stopped treatment with mepolizumab, the eosinophil counts started to increase at the follow-up visit, along with markers of asthma control. This expected response supports the need for long-term use; however, further studies are needed to determine whether a longer duration of treatment may modify the course of the disease.

A limitation of this study was the lack of a control arm; the open-label design used here means that any between-study comparisons should be made with caution. However, the observations from the open-label period reflect in-practice data on patients receiving treatment with mepolizumab.

CONCLUSIONS

A safety profile similar to that reported in previous studies was observed during long-term (52-week) treatment with subcutaneous mepolizumab.^{6,7} A durable and stable response was also demonstrated through 84 weeks of double-blind and open-label treatment. Patients previously on placebo and initiating mepolizumab treatment in this open-label extension study demonstrated improvements similar to those in MENSA and SIRIUS. These findings support the long-term use of this medicine in patients with severe eosinophilic asthma. Future long-term studies during postmarketing surveillance in clinical practice will further expand on the findings of this study.

ACKNOWLEDGMENTS

Editorial support (in the form of writing assistance, including development of the initial draft based on instruction from the authors, assembling tables and figures, collating authors' comments, grammatical editing and referencing) was provided by David Griffiths and Elizabeth Hutchinson, Fishawack Indicia Ltd (Knutsford, Cheshire, UK).

R.G. Price, S.W. Yancey, and H.G. Ortega assisted in the study design; N. Lugogo, C. Domingo, P. Chanez, and R. Leigh contributed to acquisition of the data. All of the authors had access to the study data, were involved in data analysis, provided interpretation of the data, participated in the development and review of the manuscript, and approved the final manuscript prior to submission. The decision to submit the manuscript for publication was that of the authors alone. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

CONFLICTS OF INTEREST

This research and editorial support were supported by GlaxoSmithKline (GSK; study MEA115661; ClinicalTrials.gov identifier: NCT01842607). The conception, design, and interpretation of the analysis were performed by employees of the sponsor. The sponsor did not place any restrictions on access to the data or on the statements made in the article.

R.G. Price, S.W. Yancey, and M.J. Gilson are employees of, and may own stock options in GSK. H.G. Ortega was employed by GSK during the conduct of the study, and is now employed by Genentech. N. Lugogo received grants from GSK during the conduct of the study, and has received grants from GSK, AstraZeneca, Sanofi, Genentech, and NHLBI, and advisory board fees from Teva. C. Domingo has received advisory board fees and speaker fees from Novartis, AstraZeneca, Boehringer Ingelheim, and Esteve, and support for meeting attendance from Chiesi, Menarini, Pfizer, Teva, Ferrer, ImmunoTek, ALK-Abello, Stallergenes, Allergy Therapeutics, and HAL Allergy. P. Chanez has received speaker fees, consultancy fees and advisory board fees from Almirall, Boehringer Ingelheim, Centocor, GSK, AstraZeneca, Novartis, Teva, Chiesi, and Schering-Plough, and a grant from Aix-Marseille University. R. Leigh has received consultancy or

advisory board fees from GSK, AstraZeneca, Boehringer Ingelheim, Teva, Janssen, and Novartis. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.clinthera.2016.07.010>.

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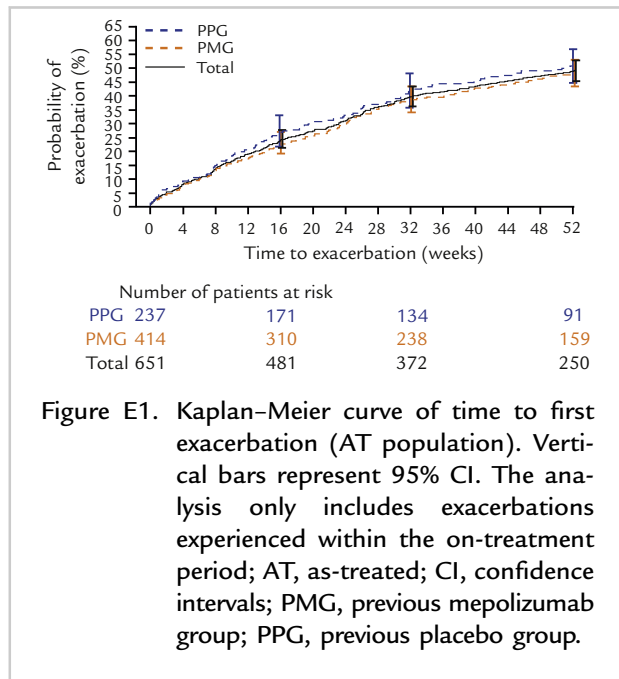
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SUPPLEMENTARY MATERIAL

Supplement to Author Disclosures

The study was conducted in accordance with GSK policy that all results, regardless of study outcome



should be published in a timely manner. Authors were in full editorial control of publication target journal, content and conclusions and accepted full responsibility for final approval of a manuscript describing this GSK sponsored research. The planning and development of publications is a scientific and medical function and GSK did not permit commercial staff to participate in the design, conduct or publication of human subject research. As agreed by authors before the preparation of the manuscript began, authors were provided with open and transparent access to data supporting publications including access to data tables, final study reports, case report forms and raw data as needed. The manuscript was prepared in line with Good Publication Practices: GSK does not pay for authorship of peer reviewed articles or presentations, although GSK may reimburse reasonable expenses associated with authorship or congress presentations (e.g. travel expenses related to attendance at author meetings or congress presentations). Notable exceptions are the use of professional medical writers: If the authors request medical writing support, this is fully disclosed in the conflict of interests section in the manuscript.

Figure E1 and Table E1.

Table E1. Probability of an exacerbation (AT population)

Time point	Probability of an exacerbation, % (95% CI)		
	PPG (N=237)	PMG (N=414)	All patients (N=651)
Week 16	26.9 (21.7, 33.0)	22.6 (18.8, 27.0)	24.2 (21.0, 27.7)
Week 32	41.6 (35.6, 48.3)	38.4 (33.9, 43.4)	39.6 (35.9, 43.6)
Week 52	50.5 (44.3, 57.1)	48.2 (43.4, 53.3)	49.1 (45.2, 53.1)

Kaplan-Meier estimates shown. The analysis only includes exacerbations experienced within the on-treatment period; AT, as-treated; CI, confidence intervals; PMG, previous mepolizumab group; PPG, previous placebo group.