Common Drug Review
Clinical Review Report

November 2016

Drug	mepolizumab (Nucala)
Indication	For the add-on maintenance treatment of adult patients with severe eosinophilic asthma who: – are inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller(s) (e.g., LABA), and – have a blood eosinophil count of ≥ 150 cells/mcL (0.15 GI/L) at initiation of treatment with mepolizumab OR ≥ 300 cells/mcL (0.3 GI/L) in the past 12 months.
Reimbursement request	For the treatment of adult patients (≥ 18 years) with severe eosinophilic asthma (≥ 150 cells/mcL at treatment initiation or ≥ 300 cells/mcL in past 12 months) whose symptoms are inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller(s), and who have either experienced ≥ 2 exacerbations in the past 12 months or have dependency on systemic corticosteroids.
Dosage form(s)	Lyophilized powder for subcutaneous injection, 100 mg/mL
NOC date	3 December 2015
Manufacturer	GlaxoSmithKline Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in respiratory disease who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

ACQ	Asthma Control Questionnaire
AE	adverse event
CI	confidence interval
FEV_1	forced expiratory volume in one second
ICS	inhaled corticosteroid(s)
ITC	indirect treatment comparison
IV	intravenous
LABA	long-acting beta agonist
MCID	minimal clinically important difference
MPPI	minimal patient perceivable improvement
OCS	oral corticosteroid(s)
OR	odds ratio
PEF	peak expiratory flow
SAE	serious adverse event
SEA	severe eosinophilic asthma
SGRQ	St. George's Respiratory Questionnaire
SC	subcutaneous
SD	standard deviation
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Asthma is a common chronic respiratory disorder characterized by reversible airway obstruction, pulmonary inflammation, airway hyperresponsiveness, and airway remodelling. Symptoms typically include wheezing, dyspnea, chest tightness, sputum production, and coughing that are associated with airflow limitation and airway hyperresponsiveness to endogenous and exogenous stimuli. It is estimated that 2.4 million Canadians aged 12 years and older have a diagnosis of asthma. Severe eosinophilic asthma (SEA) is an asthma phenotype characterized by the presence of eosinophils in the airways and sputum despite conventional asthma therapy, and it affects 5% to 10% of all asthma patients. Eosinophils are involved in the pathogenesis of asthma through the release of proinflammatory mediators at the airways, which contribute to epithelial cell damage, airway hyperresponsiveness, mucus hypersecretion, and airway remodelling.

The goal of asthma management is to maintain long-term asthma control with the least amount of medication using a stepwise approach to pharmacological therapy. Patients are started with a low-dose inhaled corticosteroid (ICS), before the addition of second-line drugs such as long-acting beta agonists (LABAs), with an increase in ICS dose if symptoms remain uncontrolled. Mepolizumab is a humanized monoclonal antibody that targets interleukin-5, a cytokine responsible for regulating eosinophil maturation, differentiation, recruitment, activation, and survival. Mepolizumab is available as a lyophilized powder for subcutaneous (SC) injection in single-use vials at 100 mg/mL after reconstitution. The Health Canada–recommended dose is 100 mg SC once every four weeks.

Indication under review
For the add-on maintenance treatment of adult patients (≥ 18 years) with severe eosinophilic asthma (≥ 150 cells/mcL at treatment initiation or ≥ 300 cells/mcL in past 12 months) whose symptoms are inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller(s).
Reimbursement criteria requested by sponsor
For the treatment of adult patients (≥ 18 years) with severe eosinophilic asthma (≥ 150 cells/mcL at treatment initiation or ≥ 300 cells/mcL in past 12 months) whose symptoms are inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller(s), and who have either experienced ≥ 2 exacerbations in the past 12 months or have dependency on systemic corticosteroids.

The objective of this review is to evaluate the beneficial and harmful effects of mepolizumab 100 mg SC for the maintenance treatment of adult patients with SEA whose symptoms are inadequately controlled with high-dose ICS and one or more additional asthma controllers).

Results and Interpretation

Included Studies

Two international, manufacturer-sponsored, phase 3, double-blind, placebo-controlled, randomized controlled trials met the inclusion criteria for this systematic review. MENSA (N = 576) was a 32-week study that evaluated the efficacy and safety of mepolizumab 100 mg SC and mepolizumab 75 mg intravenous (IV) once every four weeks as adjunctive therapy in patients with SEA. SIRIUS (N = 135) was a 24-week corticosteroid-sparing study that evaluated the effect of mepolizumab 100 mg SC once every

four weeks in reducing oral corticosteroid (OCS) use in patients with SEA. Both studies enrolled patients at least 12 years of age with documented asthma meeting specific peripheral blood eosinophil counts (≥ 150 cells/mcL at visit 1 or ≥ 300 cells/mcL in the past 12 months) who were on regular treatment with high-dose ICS and an additional controller medication (e.g., LABA, leukotriene receptor antagonist, theophylline). In SIRIUS, eligible patients were to be using OCS at a dose of between 5 mg/day and 35 mg/day. The primary end point in MENSA was the rate of clinically significant exacerbations (requiring systemic corticosteroids, hospitalization, or emergency department visits) at week 32. The primary end point in SIRIUS was the percentage reduction of OCS dose during weeks 20 to 24 compared with baseline dose while maintaining asthma control. Secondary end points in MENSA included the change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) and the change from baseline in St. George's Respiratory Questionnaire (SGRQ) at week 32. Change from baseline in Asthma Control Questionnaire (ACQ-5) scores, morning peak expiratory flow (PEF), rescue medication use, and nighttime awakenings were evaluated as exploratory end points in MENSA. In SIRIUS, secondary end points included the proportion of patients achieving specific OCS dose reductions (≥ 50% reduction, reduction to ≤ 5.0 mg/day, and total reduction) and median percentage reduction from baseline. In SIRIUS, clinical outcomes such as exacerbations, quality of life, and symptoms were evaluated as exploratory end points. Patients who completed the MENSA and SIRIUS trials had the option of participating in a 12-month open-label safety study (MEA115661, N = 651), where all patients received mepolizumab 100 mg SC once every four weeks.

Limitations of MENSA and SIRIUS included the relatively short duration of the studies to evaluate asthma exacerbations, the potential for improved compliance to background therapy in a clinical trial setting compared with real life as evidenced by improvements in the placebo groups, and the uncertainty regarding appropriate selection criteria to identify SEA patients.

Efficacy

The rate of clinically significant exacerbations (requiring treatment with systemic corticosteroids for greater than or equal to three days, hospitalization, or emergency department visit) was the primary end point in MENSA. The rate of clinically significant exacerbations was statistically significantly lower in the mepolizumab group than in the placebo group in MENSA (rate ratio 0.47; 95% confidence interval [CI], 0.35 to 0.64; $P < 0.001$). In MENSA, the rate of exacerbations requiring hospitalization or emergency department visit was statistically significantly lower in the mepolizumab group compared with the placebo group (rate ratio 0.39; 95% CI, 0.18 to 0.83; $P = 0.015$). The rate of exacerbations requiring hospitalization was lower in the mepolizumab group compared with the placebo group (rate ratio 0.31; 95% CI, 0.11 to 0.91; $P = 0.034$); however, this outcome was analyzed as exploratory based on the analysis hierarchy for control of multiplicity. The clinical expert noted that a 52-week or longer study would be better to assess asthma exacerbations, as exacerbations fluctuate with changing seasons in Canada.

Patients with severe asthma may require regular treatment with OCS, and long-term use of OCS may be accompanied by adverse side effects including weight gain, hypertension, osteoporosis, diabetes, and cardiovascular disease. In both MENSA and SIRIUS, similar proportions of exacerbations were treated with OCS, and each treatment course was for a similar number of days across the mepolizumab and placebo groups. As there were more exacerbations in the placebo groups than in the mepolizumab groups (MENSA, 216 versus 116; SIRIUS, 68 versus 47), the placebo groups had a greater usage of OCS to manage acute exacerbations. In SIRIUS, the primary end point was the percentage reduction of OCS dose during weeks 20 to 24 compared with baseline dose while maintaining asthma control. In SIRIUS, the odds ratio (OR) of mepolizumab to placebo of achieving a percentage reduction from baseline in

OCS dose was statistically significant (OR 2.39; 95% CI, 1.25 to 4.56; *P* = 0.008). A statistically significantly greater proportion of patients achieved a ≥ 50% reduction in daily OCS dose in the mepolizumab group compared with the placebo group (OR 2.26; 95% CI, 1.10 to 4.65; *P* = 0.027). A statistically significantly greater proportion of patients achieved a reduction in daily OCS dose to ≤ 5 mg in the mepolizumab group compared with the placebo group (OR 2.45; 95% CI, 1.12 to 5.37; *P* = 0.025). More patients in the mepolizumab group achieved a total reduction in OCS dose compared with the placebo group, but this difference was not statistically significant (OR 1.67; 95% CI, 0.49 to 5.75; *P* = 0.414). There was a statistically significant median percentage reduction from baseline in daily OCS dose in the mepolizumab group compared with the placebo group (median difference −30.0; 95% CI, –66.7 to 0.0; *P* = 0.007). The clinical expert noted that the titration schedule was rather aggressive for patients with a starting OCS dose of 25 mg/day to 35 mg/day, with large incremental reductions in the first few weeks, but that results suggested meaningful reductions in OCS dose with mepolizumab.

Pulmonary function as measured by FEV_1 and PEF are widely used to assess the efficacy of drug treatments for asthma in clinical trials, and pre-bronchodilator FEV_1 has been considered to be the most suitable variable when measuring asthma control. In both trials, the statistical analyses of these outcomes were considered exploratory. In MENSA, the mean change from baseline pre-bronchodilator FEV_1 at week 32 was statistically significantly greater in the mepolizumab group than in the placebo group (mean difference 98 mL; 95% CI, 11 to 184; *P* = 0.028). In SIRIUS, there was no clear improvement from baseline at week 24 in pre-bronchodilator FEV_1 (mean difference 114 mL; 95% CI, –42 to 271). Change from baseline in morning PEF at end of study was reported descriptively as four-week aggregated data in both studies, and a greater improvement was seen in the mepolizumab group compared with the placebo group (MENSA, mean difference 29.5 [standard deviation (SD) 69.0] L/min; SIRIUS, mean difference 19.1 [SD 56.2] L/min).

Health-related quality of life was another key efficacy outcome, and patients with severe asthma stated that their day-to-day lives were affected by the disease. In MENSA and SIRIUS, quality of life was measured using the SGRQ, which was developed to assess impaired health and perceived well-being in patients with chronic airflow limitation and has a reported minimal clinically important difference (MCID) of four points. In MENSA, there was a statistically significantly greater improvement in SGRQ total score at week 32 in the mepolizumab group compared with the placebo group (mean difference –7.0; 95% CI, –10.2 to –3.8; *P* < 0.001). In SIRIUS, there was a greater improvement in SGRQ total score at week 24 in the mepolizumab group compared with the placebo group (mean difference –5.8; 95% CI, –10.6 to –1.0). In both studies, a greater proportion of patients in the mepolizumab group achieved a greater than or equal to four-point improvement in SGRQ total score at the end of the double-blind period compared with placebo (MENSA, 71% versus 55%; SIRIUS, 58% versus 41%). Statistical analyses of health-related quality of life outcomes were considered exploratory.

While current therapies do provide some relief from symptoms, patients expressed a desire for improved control of asthma symptoms with new therapies. In MENSA and SIRIUS, the ACQ-5 was used to assess symptom control; ACQ-5 is a shortened version of the full ACQ containing only five items on asthma symptoms with an estimated MCID of 0.5. Higher ACQ-5 scores indicate poor asthma control. In MENSA and SIRIUS, there was a greater improvement from baseline in ACQ-5 total score at week 32 in the mepolizumab group than in the placebo group (MENSA, mean difference –0.44; 95% CI, −0.63 to –0.25; SIRIUS, mean difference –0.52; 95% CI, –0.87 to –0.17).

Patients expressed how asthma symptoms impacted them negatively through increased emergency room visits in the past year and reduced performance at work or school. In MENSA and SIRIUS, the

proportion of exacerbations requiring emergency room visits or doctor visits was similar between the mepolizumab and placebo groups, but because of the higher number of exacerbations in the placebo groups compared with the mepolizumab groups (MENSA, 216 versus 116; SIRIUS, 68 versus 47), unscheduled resource use was higher in the placebo group. With regard to days taken off school and work due to asthma symptoms, numbers were generally low and were balanced between the mepolizumab and placebo groups in both studies, with the exception of days off work in SIRIUS, where placebo patients had a higher mean days off work than the mepolizumab group (5.7 versus 2.5).

Because there were no direct head-to-head trials of mepolizumab and other therapies for severe asthma identified in this review, the manufacturer submitted an indirect treatment comparison (ITC) to evaluate the relative efficacy of mepolizumab and omalizumab in patients with severe asthma who would be eligible for both therapies— namely, patients with allergic asthma with an eosinophilic component. The results of the ITC suggested that [redacted]. However, there are very serious limitations with the analysis and a high degree of uncertainty associated with the ITC findings. Therefore, no conclusion can be drawn regarding the comparative effectiveness and safety of mepolizumab with omalizumab in the treatment of severe asthma.

Harms

In MENSA, a total of 78% of patients in the mepolizumab group and 83% of patients in the placebo group reported an adverse event (AE) during the 32-week double-blind treatment period. In SIRIUS, a total of 83% of patients in the mepolizumab group and 92% of patients in the placebo group reported an AE during the 24-week double-blind OCS dose reduction treatment period. Common AEs included nasopharyngitis, headache, upper respiratory tract infections, asthma, sinusitis, bronchitis, and fatigue. The incidence of asthma exacerbations and worsening was higher in the placebo groups than in the mepolizumab groups. In both trials, the proportion of patients reporting a serious adverse event (SAE) was higher in the placebo groups than in the mepolizumab groups (MENSA, 14% versus 8%; SIRIUS, 18% versus 1%). The most common AE was asthma exacerbation or worsening. In MENSA, one patient (< 1%) in the mepolizumab group and four patients (2%) in the placebo group withdrew due to an AE. In SIRIUS, three patients in each group withdrew due to an AE. There was no clear pattern of reason for withdrawal due to an AE (WDAE) in any group.

Injection-site reactions were low across groups but slightly more common in the mepolizumab group than in the placebo group (MENSA, 9% versus 3%; SIRIUS, 6% versus 3%). All injection-site reactions were reported as mild or moderate in intensity. Systemic allergic reactions were low and balanced across the mepolizumab and placebo groups in both trials (MENSA, 2% for both groups; SIRIUS, 6% versus 5%). Serious infections were reported in 3% of patients in both treatment groups in MENSA and in 1% of patients in the mepolizumab group and 6% of patients in the placebo group in SIRIUS. Opportunistic infection was reported in 2% of patients in the mepolizumab group in MENSA and 2% of patients in the placebo group in SIRIUS. Cardiac disorders were balanced and low across the mepolizumab and placebo groups (MENSA, 2% versus 3%; SIRIUS, 3% versus 5%). Malignant neoplasms were reported in three patients (5%) in the placebo group in SIRIUS and in no patients in the remaining groups.

Patients who completed MENSA and SIRIUS had the option of enrolling in a 52-week open-label extension study (MEA115666, [redacted]) where they received mepolizumab 100 mg SC once every four

weeks. [redacted].

Conclusions

Two international, manufacturer-sponsored, phase 3, double-blind, placebo-controlled, randomized controlled trials met the inclusion criteria for this systematic review. MENSA (N = 576) was a 32-week study that evaluated the efficacy and safety of mepolizumab 100 mg SC and mepolizumab 75 mg IV once every four weeks as adjunctive therapy in patients with SEA. SIRIUS (N = 135) was a 24-week corticosteroid-sparing study that evaluated the effect of mepolizumab 100 mg SC once every four weeks in reducing OCS use in patients with SEA. Results from MENSA suggested that mepolizumab 100 mg SC is associated with a statistically significant reduction in the rate of clinically significant asthma exacerbations compared with placebo in patients currently on high-dose ICS and an additional asthma controller meeting screening eosinophil criteria of ≥ 150 cells/mcL at screening or ≥ 300 cells/mcL in the past year. Results from SIRIUS suggested that mepolizumab 100 mg SC is associated with a greater likelihood of a reduction in daily OCS dose compared with placebo in patients with SEA who were taking OCS at a dose of 5 mg/day to 35 mg/day. Due to the increased number of exacerbations in the placebo groups compared with the mepolizumab groups, there was greater unplanned health resource use and OCS use in the placebo groups. Adverse event data were generally similar between groups, except for a higher proportion of patients in the placebo groups experiencing asthma-related AEs than in the mepolizumab groups. [redacted].

There were no direct head-to-head trials of mepolizumab and other therapies for severe asthma identified in this review. The manufacturer submitted an ITC to evaluate the relative efficacy of mepolizumab and omalizumab in patients with severe asthma who would be eligible for both therapies. [redacted]. However, there were serious limitations with the analyses due to the limited number of studies included and a high degree of uncertainty associated with the findings.

TABLE 1: SUMMARY OF RESULTS

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Clinically Significant Exacerbations — MENSA Primary End Point				
Number of patients, n (%)	64 (33)	105 (55)	29 (42)	45 (68)
Number of exacerbations	116	216	47	68
Exacerbation rate/year	0.83	1.74	1.44	2.12
Rate ratio (95% CI), *P* value[a]	0.47 (0.35 to 0.64), < 0.001		0.68 (0.47 to 0.99)	
Exacerbations Requiring Hospitalization or ED Visit				
Number of patients, n (%)	11 (6)	24 (13)	3 (4)	7 (11)
Number of exacerbations	20	33	3	9
Exacerbation rate/year	0.08	0.20	–[b]	–
Rate ratio (95% CI), *P* value[a]	0.39 (0.18 to 0.83), *P* = 0.015		–[b]	
Exacerbations Requiring Hospitalization				
Number of patients, n (%)	5 (3)	13 (7)	0	7 (11)
Number of exacerbations	9	18	0	8
Exacerbation rate/year	0.03	0.10	–[b]	–
Rate ratio (95% CI), *P* value[a]	0.31 (0.11 to 0.91), *P* = 0.034[c]		–[b]	
Reduction From Baseline in OCS Dose, n (%) – SIRIUS Primary End Point				
OR vs. placebo (95% CI), *P* value[d]	NA	NA	2.39 (1.25 to 4.56), *P* = 0.008	
≥ 50% Reduction in Daily OCS Dose, n (%)				
OR vs. placebo (95% CI), *P* value[d]	NA	NA	2.26 (1.10 to 4.65), *P* = 0.027	
Reduction in Daily OCS Dose to ≤ 5 mg, n (%)				
OR vs. placebo (95% CI), *P* value[d]	NA	NA	2.45 (1.12 to 5.37), *P* = 0.025	
Total Reduction in OCS Dose, n (%)				
OR vs. placebo (95% CI), *P* value[d]	NA	NA	1.67 (0.49 to 5.75), *P* = 0.414	
Median Percentage Reduction in Daily OCS Dose (%)				
Mean difference (95% CI), *P* value[e]			–30.0 (–66.7 to 0.0), *P* = 0.007	
Pre-bronchodilator FEV_1, mL				
Baseline mean (SD)	1,730 (659.2)	1,860 (630.8)	1,897 (660.2)	2,005 (822.3)
LS mean change (SE)	183 (31.1)	86 (31.4)	111 (55.1)	–4 (56.5)
Difference (95% CI), *P* value[a]	98 (11 to 184), *P* = 0.028[f]		114 (–42 to 271)	
Morning PEF, L/min				
Baseline mean (SD)	255.3 (107.6)	277.0 (105.5)	284.7 (124.8)	311.9 (152.3)
Mean change from baseline (SD)	29.5 (69.0)	1.8 (58.9)	19.1 (56.2)	4.1 (47.0)
SGRQ Total Score				
Baseline mean (SD)	47.9 (19.5)	46.9 (19.8)	49.6 (17.8)	45.0 (18.4)
LS mean change (SE)	–16.0 (1.1)	–9.0 (1.2)	–8.8 (1.7)	–3.1 (1.7)

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Difference (95% CI), *P* value[a]	–7.0 (–10.2 to –3.8), *P* < 0.001[f]		–5.8 (–10.6 to –1.0)	
≥ 4 point improvement, n (%)	137 (71)	105 (55)	40 (58)	27 (41)
ACQ-5 Total Score				
Baseline mean (SD)	2.26 (1.27)	2.28 (1.19)	2.15 (1.27)	1.99 (1.18)
LS mean change (SE)	–0.94 (0.07)	–0.50 (0.07)	–0.61 (0.13)	–0.09 (0.13)
Difference (95% CI)[a]	–0.44 (–0.63 to –0.25)		–0.52 (–0.87 to –0.17)	
Harms				
Patients with > 0 AEs, n (%)	152 (78)	158 (83)	57 (83)	61 (92)
Patients with > 0 SAEs, n (%)	16 (8)	27 (14)	1 (1)	12 (18)
Patients with > 0 WDAEs, n (%)	1 (< 1)	4 (2)	3 (4)	3 (5)
Notable Harms, n (%)				
Injection-site reaction	17 (9)	6 (3)	4 (6)	2 (3)
Systemic allergic reaction	3 (2)	4 (2)	4 (6)	3 (5)
Serious infection	6 (3)	5 (3)	1 (1)	4 (6)
Opportunistic infection	3 (2)	0	0	1 (2)
Cardiac disorder	4 (2)	5 (3)	2 (3)	3 (5)
Malignancy	0	0	0	3 (5)

ACQ-5 = Asthma Control Questionnaire 5; AE = adverse event; CI = confidence interval; ED = emergency department; FEV_1 = forced expiratory volume in 1 second; LS = least squares; NA = not assessed; OCS = oral corticosteroid; OR = odds ratio; PEF = peak expiratory flow; SAE = serious adverse event; SC = subcutaneous; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; vs. = versus; WDAE = withdrawal due to adverse event.
Note: Mean change results are presented for the end of the treatment period (32 weeks in MENSA, 24 weeks in SIRIUS).
[a] Generalized linear model with covariates for treatment, region, baseline maintenance OCS therapy, number of exacerbations in the past year, and baseline disease severity (% predicted FEV_1) in SIRIUS; covariates for treatment, region, duration of OCS use at baseline (< 5 years versus ≥ 5 years, and dose of OCS at baseline in MENSA.
[b] Insufficient events to perform analysis.
[c] Descriptive as outcome fell below a non-statistically significant parameter in the testing hierarchy.
[d] Binary logistic regression with covariates for treatment group, region, duration of OCS use at baseline (< 5 years vs. ≥ 5 years), and baseline OCS dose.
[e] Median difference and CI derived using Hodges-Lehman estimation; *P* value derived using a Wilcoxon rank-sum test; missing data imputed using the minimum percentage reduction in OCS.
[f] Cox proportional hazards model with same covariates as mentioned in footnote b.
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Asthma is a common chronic respiratory disorder characterized by reversible airway obstruction, pulmonary inflammation, airway hyperresponsiveness and airway remodelling.[3,4] Described by a range of heterogeneous phenotypes, symptoms may differ by presentation, etiology, and pathophysiology. Patients with asthma typically present with paroxysmal or persistent symptoms of wheezing, dyspnea, chest tightness, sputum production, and coughing that are associated with airflow limitation and airway hyperresponsiveness to endogenous and exogenous stimuli (e.g., exercise, viral respiratory infections, or exposure to certain allergens, irritants, or gases).[4] Although asthma can be diagnosed at any age, it often starts in childhood. In 2015, Statistics Canada estimated that 2.4 million Canadians 12 years and older had a diagnosis of asthma,[5] representing 12% of all Canadian children and 8% of all Canadian adults.[5]

Severe eosinophilic asthma (SEA) is an asthma phenotype characterized by the presence of eosinophils in the airways and sputum despite proper compliance to conventional asthma therapy.[6] Eosinophils are mediators of the allergic inflammatory response and contribute to airway hyperresponsiveness and remodelling.[6,7] Tissue eosinophilia is present in 40% to 60% of patients with asthma, and conventional therapies with inhaled corticosteroids (ICS) typically reduce total airway eosinophils in these patients.[6] However, 5% to 10% of all asthma patients (50% of severe asthmatics) continue to experience exacerbations and symptoms with persistent airway eosinophils despite high-dose ICS.[6]

1.2 Standards of Therapy

Given its heterogeneous phenotypes, the treatment for asthma is individualized to each patient's unique circumstances and customized as necessary. The primary goals of asthma management include long-term maintenance of asthma control[4] with the least amount of medication and minimization of adverse events (AEs).[8] Asthma control, in the Canadian Thoracic Society guidelines, is based on several characteristics, including:

- Frequency of daytime and nighttime symptoms
- Frequency of exacerbations
- Frequency of absences from work or school due to asthma
- Ability to complete normal physical activity
- Need for a fast-acting beta$_2$ agonist
- Forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF)
- PEF diurnal variation
- Sputum eosinophils.[4]

Asthma control may prevent or minimize the risks to short-term and long-term complications, further morbidity, and death.[4] It has been reported that much of asthma-related morbidity is associated with poor management resulting from underused maintenance therapy or poor adherence to maintenance therapy.[9]

According to the guidelines published by the Canadian Thoracic Society, a stepwise approach to pharmacological therapy is recommended to achieve and maintain asthma control.[4] This involves escalating pharmacological treatment as necessary to gain control (i.e., stepping up) and then reducing treatment (i.e., stepping down) to the minimum required with respect to dose and number of medications for maintenance.[4] Current Canadian and international guidelines recommend that patients with asthma in all age groups be initiated with low-dose ICS.[4,10] If control is not gained or maintained,

second-line drugs may be added, such as a long-acting beta$_2$ agonist (LABA) or leukotriene receptor antagonist, or the ICS dose can be titrated upward.[4] For individuals whose asthma remains uncontrolled on ICS plus LABA, a further increase in ICS dose or the addition of leukotriene receptor antagonists is recommended. For a specific subset of patients with uncontrolled asthma on high-dose ICS who exhibit a positive skin test or in vitro reactivity to a perennial aeroallergen, omalizumab, an anti-immunoglobulin E antibody, may be an option.

1.3 Drug

Mepolizumab is a humanized monoclonal antibody that targets interleukin-5, a cytokine responsible for regulating eosinophil maturation, differentiation, recruitment, activation, and survival. Eosinophils are involved in the pathogenesis of asthma through the release of proinflammatory mediators at the airways, which contribute to epithelial cell damage, airway hyperresponsiveness, mucus hypersecretion, and airway remodelling. Mepolizumab is available as a lyophilized powder for subcutaneous (SC) injection in single-use vials at 100 mg/mL after reconstitution. The Health Canada–recommended dose is 100 mg SC once every four weeks.

Indication under review
For the add-on maintenance treatment of adult patients (≥18 years) with severe eosinophilic asthma (≥150 cells/mcL at treatment initiation or ≥ 300 cells/mcL in past 12 months) whose symptoms are inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller(s).
Reimbursement criteria requested by sponsor
For the treatment of adult patients (≥ 18 years) with severe eosinophilic asthma (≥ 150 cells/mcL at treatment initiation or ≥300 cells/mcL in past 12 months) whose symptoms are inadequately controlled with high-dose inhaled corticosteroids and an additional asthma controller(s), and who have either experienced ≥ 2 exacerbations in the past 12 months or have dependency on systemic corticosteroids.

TABLE 2: KEY CHARACTERISTICS OF MEPOLIZUMAB AND OMALIZUMAB

	Mepolizumab	Omalizumab
Mechanism of Action	Anti-IL-5 antibody	Anti-IgE antibody
Indication[a]	For the add-on maintenance treatment of adult patients (≥ 18 years) with SEA (≥ 150 cells/mcL at treatment initiation or ≥ 300 cells/mcL in past 12 months) whose symptoms are inadequately controlled with high-dose ICS and an additional asthma controller(s)	For the treatment of adults and adolescents (≥ 12 years) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled on ICS
Route of Administration	SC	SC
Recommended Dose	100 mg every 4 weeks	150 mg to 375 mg every 2 or 4 weeks depending on body weight and serum IgE level
Serious Side Effects or Safety Issues	Injection-site reactions, infection, systemic allergic reaction	Anaphylaxis, injection-site reactions, infection

ICS = inhaled corticosteroids; IgE = immunoglobulin E; IL-5 = interleukin-5; SC = subcutaneous; SEA = severe eosinophilic asthma.
[a] Health Canada indication.
Source: Nucala product monograph,[11] Xolair product monograph.[12]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of mepolizumab for the treatment of adult patients (≥ 18 years) with SEA (≥ 150 cells/mcL at treatment initiation or ≥ 300 cells/mcL in the past 12 months) whose symptoms are inadequately controlled with high-dose ICS and one or more additional asthma controllers.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults (≥ 18 years) with SEA whose symptoms are inadequately controlled with high-dose ICS and an additional asthma controller(s) Subgroups of interest: • Baseline asthma control medication • Baseline peripheral eosinophil count • Baseline IgE levels • Number of exacerbations in past 12 months • Use of rescue medications • Previous use of omalizumab • Diagnosis of allergic asthma
Intervention	Mepolizumab 100 SC mg every 4 weeks, as add-on therapy to a high-dose ICS and an additional asthma controller(s)
Comparators	LABA LTRA LABA + LAMA LABA + LTRA Omalizumab Chronic OCS ICS would be used in combination with all medications. Rescue medication (e.g., SABA, SAMA) may be used for acute exacerbations.
Outcomes	***Key efficacy outcomes:*** • Health care resource use (i.e., hospitalizations,[a] ED visits,[a] MD visits[a]) • Acute asthma exacerbations[a] • Use of OCS[a] • Quality of life as measured by a validated scale[a] • Days of missed school or work[a] • Change in pulmonary function (e.g., PEF, FEV_1) ***Other efficacy outcomes:*** • Symptom reduction (e.g., ACQ)[a] • Change in number of asthma symptom–free days or nights[a] • Incidence of nocturnal awakenings[a] • Reduction of use of ICS • Reduction of use of rescue medication

	Mortality **Harms outcomes:** • AEs, SAEs, WDAEs • Notable harms/harms of special interest: cardiovascular AEs, opportunistic infection, injection-site reactions, malignancies, systemic allergic reactions
Study Design	Published and unpublished phase 3 RCTs

ACQ = Asthma Control Questionnaire; AE = adverse event; ED = emergency department; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; IgE = immunoglobulin E; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; MD = medical doctor; OCS = oral corticosteroids; PEF = peak expiratory flow; RCT = randomized controlled trial; SABA = short-acting beta agonist; SAE = serious adverse event; SAMA = short-acting muscarinic antagonist; SC = subcutaneous; SEA = severe eosinophilic asthma; WDAE = withdrawal due to adverse event.
[a] Important outcomes indicated by patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with In-Process Records & Daily Updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were **Nucala (mepolizumab), Interleukin-5, and asthma.**

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on January 25, 2016. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on May 18, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

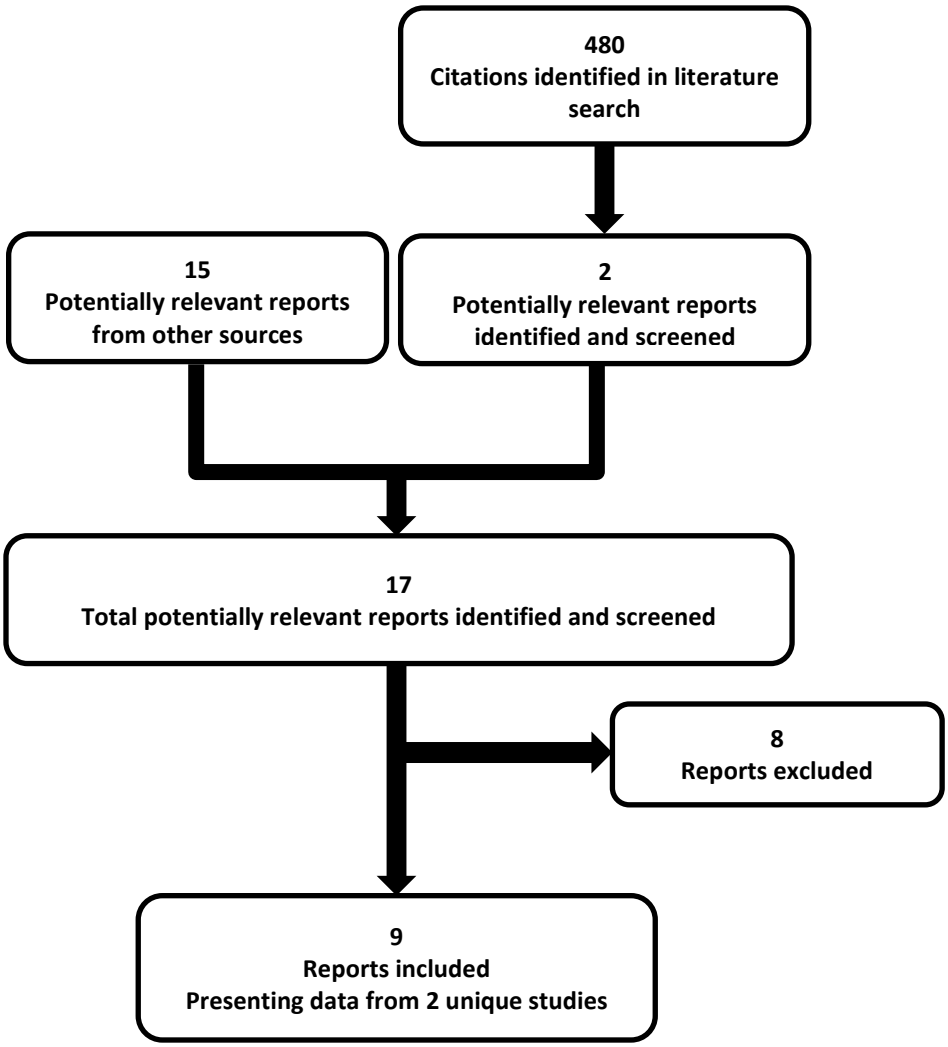


TABLE 4: DETAILS OF INCLUDED STUDIES

		MENSA (MEA115588)	SIRIUS (MEA115575)
DESIGNS AND POPULATIONS	**Study Design**	DB DD PC PG RCT	DB PC PG RCT
	Locations	119 centres in 16 countries: Canada (10), US, Australia, South America, Europe, Asia	38 centres in 10 countries: Canada (3), US, Australia, Europe
	Randomized (N)	576	135

	Inclusion Criteria	• Patients ≥ 12 years and ≥ 45 kg with SEA
		  ○ Peripheral blood eosinophil count ≥ 150 cells/mcL at visit 1 *or* ≥ 300 cells/mcL in past 12 months
		  ○ Asthma documented within past 12 months: airway reversibility of FEV ≥ 12% and ≥ 200 mL *or* airway hyperresponsiveness *or* airflow variability FEV_1 ≥ 20% between two clinic visits *or* diurnal airflow variability PEF > 20% on ≥ 3 days
		  ○ Persistent airflow obstruction: FEV_1 < 80% predicted in patients ≥ 18 years; FEV_1 < 90% predicted or FEV_1: FVC < 0.8 in patients 12 to 17 years
		• Regular treatment with high-dose ICS (≥ 880 µg/day FP or equivalent in patients ≥ 18 years; ≥ 440 µg/day FP or equivalent in patients 12 years to 17 years) in previous 12 months (MENSA) or 6 months (SIRIUS) and a requirement for additional controller medication (LABA, LTRA, or theophylline) for ≥ 3 successive months	

		• Background treatment may be with or without OCS	• Requirement for regular treatment with OCS (5 to 35 mg/day prednisone or equivalent)
	Exclusion Criteria	• Current or former smokers (≥ 10 pack-years) • Other clinically important lung conditions • Previous history of cancer in remission < 12 months • Uncontrolled clinically significant cardiovascular disease • Hypereosinophilic syndromes (e.g., Churg-Strauss) • Use of omalizumab within 130 days	
DRUGS	**Intervention**	Mepolizumab 100 mg SC once every 4 weeks	
	Comparator(s)	Mepolizumab 75 mg IV once every 4 weeks Placebo (0.9% sodium chloride)	Placebo (0.9% sodium chloride)
DURATION	**Phase**		
	Run-in	1 to 6 weeks	3 to 8 weeks (optimize OCS dose)
	Double-blind	32 weeks	24 weeks (4 weeks' induction, 16 weeks' OCS reduction, 4 weeks' maintenance)
	Follow-up	8 weeks	8 weeks
OUTCOMES	**Primary End Point**	Frequency of asthma exacerbations requiring systemic CS, hospitalization or ED visits	Percentage reduction of OCS dose during weeks 20 to 24 compared with baseline dose, while maintaining asthma control
	Other End Points	**Secondary** • Frequency of exacerbations requiring hospitalization or ED visits • Frequency of exacerbations requiring hospitalization	**Secondary** • Proportion of patients who achieved a ≥ 50% reduction in daily OCS dose • Proportion of patients who achieved a reduction of OCS dose to ≤ 5.0 mg

		MENSA (MEA115588)	SIRIUS (MEA115575)
		• Mean change from baseline in clinic pre-bronchodilator FEV_1 at week 32 • Mean change from baseline in SGRQ at week 32 *Other* • Mean change from baseline in ACQ-5 score at week 32 • Mean change from baseline in morning PEF • Mean change from baseline in daily salbutamol/albuterol use • Mean number of days with OCS taken for exacerbations	• Proportion of patients who achieved a total reduction of OCS dose • Median percentage reduction from baseline in daily OCS dose *Other* • Rate of clinically significant exacerbations • Rate of exacerbations requiring hospitalization or ED visits • Rate of exacerbations requiring hospitalization • Mean change from baseline in SGRQ at week 24 • Mean change from baseline in ACQ-5 at week 24 • Mean change from baseline in daily salbutamol/albuterol use • Mean change from baseline in daily asthma symptom scores • Mean number of days with OCS taken for exacerbations
NOTES	**Publications**	Ortega et al. 2014[13]	Bel et al. 2014[14]

ACQ-5 = Asthma Control Questionnaire 5; CS = corticosteroids; DB = double blind; DD = double dummy; ED = emergency department; FEV_1 = forced expiratory volume in 1 second; FP = fluticasone propionate; FVC = forced vital capacity; ICS = inhaled corticosteroids; IV = intravenous; LABA = long-acting $beta_2$ agonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroids; PC = placebo controlled; PEF = peak expiratory flow; PG = parallel group; RCT = randomized controlled trial; SC = subcutaneous; SEA = severe eosinophilic asthma; SGRQ = St. George's Respiratory Questionnaire.
Note: 5 additional reports were included: Health Canada Reviewer's Report,[15] FDA Medical Review,[16] FDA Statistical Review,[17] EMA Public Assessment Report,[18] CADTH Common Drug Review Submission.[19]
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

3.2 Included Studies

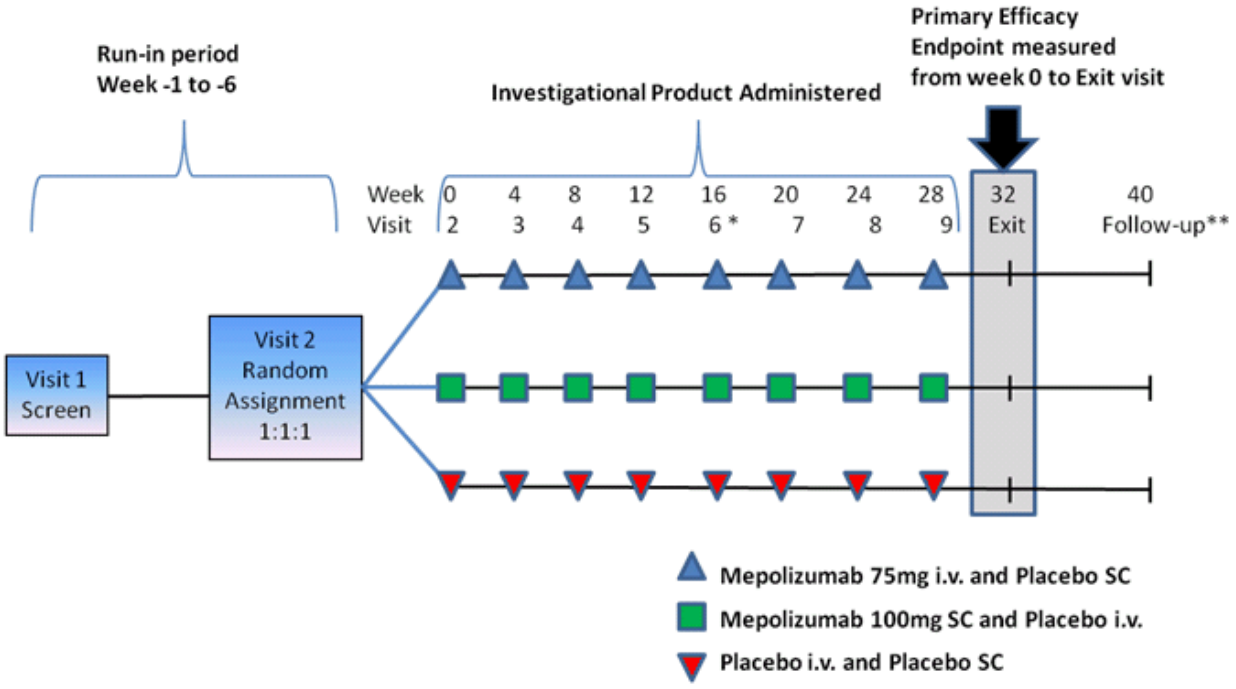
3.2.1 Description of Studies

Two phase 3, multi-centre, multinational, double-blind, placebo-controlled, superiority randomized trials met the inclusion criteria for this systematic review. MENSA (N = 576) was a 32-week study that evaluated the efficacy and safety of mepolizumab 100 mg SC and mepolizumab 75 mg intravenous (IV) once every four weeks as adjunctive therapy in patients with SEA. In MENSA, patients had a run-in period for at least one week to six weeks before being randomized in a 1:1:1 ratio to receive mepolizumab 100 mg SC, mepolizumab 75 mg IV, or placebo for 32 weeks, with treatments being administered in a double dummy fashion.

SIRIUS (N = 135) was a 24-week corticosteroid-sparing study that evaluated the effect of mepolizumab 100 mg SC once every four weeks in reducing oral corticosteroid (OCS) use in patients with SEA. In SIRIUS, eligible patients who were currently using OCS at a dose between 5 mg/day and 35 mg/day went through a three-week to eight-week optimization phase where OCS dose adjustments were made every week to determine the lowest effective dose of OCS before the occurrence of an exacerbation. After the optimization phase, patients were randomized in a 1:1 ratio, stratified by prior duration of OCS use (≥ 5 years and < 5 years), to receive mepolizumab 100 mg SC or placebo. One dose of study medication was

administered during the four-week induction phase to allow sufficient time for patients in the mepolizumab group to decrease eosinophilic inflammation before OCS reduction. After the induction phase, patients entered the 16-week OCS reduction phase, during which OCS doses were gradually reduced every four weeks according to a titration schedule, before entering a four-week maintenance phase, during which no more OCS dose adjustments were made.

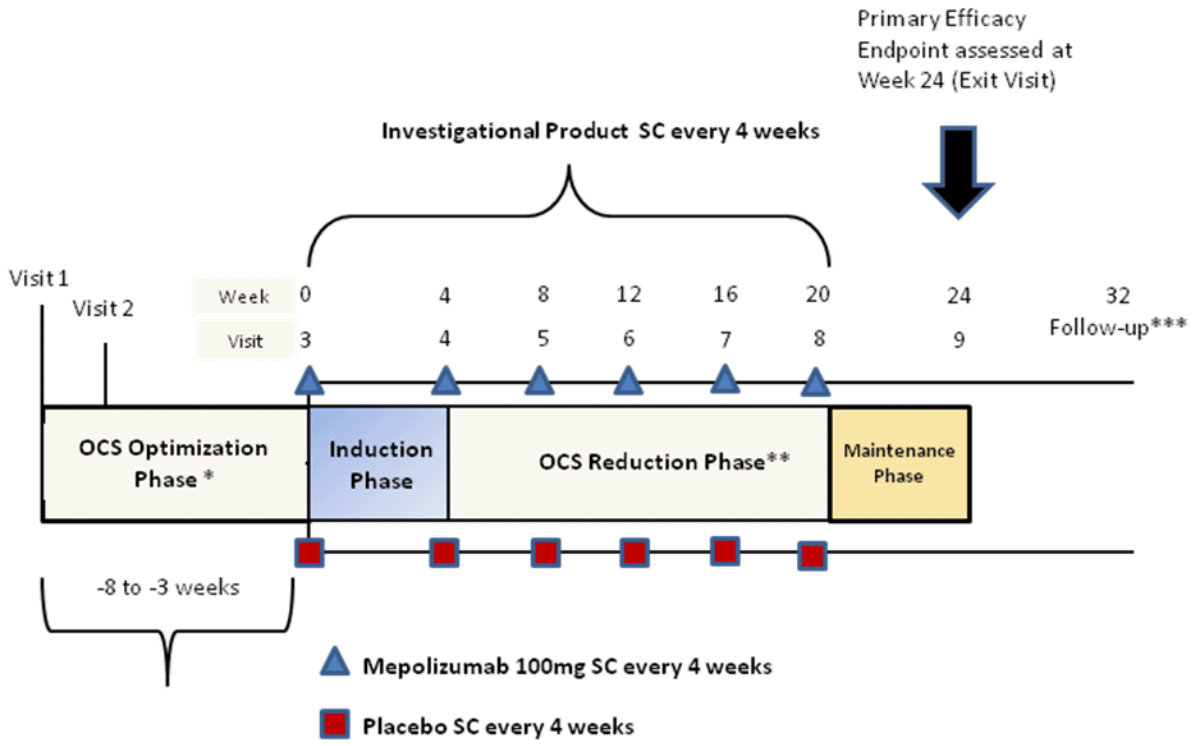
FIGURE 2: MENSA STUDY DESIGN



* Subjects in a sub-set of countries will return 3-10 days post visit 6 to obtain a PK sample
** Only subjects not entering the open label extension study will complete the Follow-up Visit

i.v. = intravenous; SC = subcutaneous.
Source: MENSA Clinical Study Report.[1]

FIGURE 3: SIRIUS STUDY DESIGN



*The OCS Optimization Phase could be extended to 10 weeks if a subject experienced an exacerbation during this phase.
** OCS dose titration occurred throughout the Optimization and Reduction Phases of the study. OCS titration did not necessarily coincide with the Visits scheduled for investigational product administration as indicated above.
*** Only subjects who did not enter the open label extension (OLE) study completed the Follow-up Visit at 12 weeks post last dose

OCS = oral corticosteroid; SC = subcutaneous.
Source: SIRIUS Clinical Study Report.[2]

The primary efficacy end point for both studies was assessed four weeks after the last dose of study medication was administered, with an additional follow-up visit 12 weeks after the last dose. Patients who completed the MENSA and SIRIUS trials had the option of participating in a 12-month open-label safety study (MEA115661, N = 651), where all patients received mepolizumab 100 mg SC once every four weeks (APPENDIX 6).

The Health Canada–approved dose and route of administration for mepolizumab are 100 mg SC once every four weeks; therefore, only trials that included this dosing regimen were included in this review. A phase 2/3 study (DREAM, N = 616) evaluated the efficacy and safety of various IV doses of mepolizumab and is summarized in APPENDIX 7.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Both MENSA and SIRIUS included adolescent and adult patients at least 12 years of age weighing at least 45 kg with a diagnosis of SEA based on peripheral blood eosinophil counts (≥ 150 cells/mcL at visit 1 or ≥ 300 cells/mcL in the past 12 months), persistent airflow obstruction, and documented asthma as indicated by airway reversibility, airway hyperresponsiveness, or airflow variability. Patients were to be

on regular treatment with high-dose ICS in the past 12 months (MENSA) or 6 months (SIRIUS) with an additional controller medication for at least 3 successive months in the past 12 months. In MENSA, background treatment could be with or without OCS, while in SIRIUS, patients had to be on regular treatment with OCS at a dose of 5 mg/day to 35 mg/day prednisone or equivalent.

In both studies, patients were excluded if they were current or former smokers with a smoking history of at least 10 pack-years or if they had other clinically important lung conditions, hypereosinophilic syndromes, a history of cancer, or uncontrolled cardiovascular disease. Patients were also excluded if they had used omalizumab within 130 days before visit 1.

b) Baseline Characteristics

Baseline demographics and disease characteristics are summarized in Table 5. More than half the patients were female and the majority of patients were white. In MENSA, approximately 19% of patients were of Asian descent. Almost all enrolled patients were at least 18 years of age, with fewer than 5% of patients in MENSA and two patients in SIRIUS who were between the ages of 12 years and 17 years. In MENSA, the proportion of females was greater in the mepolizumab group than in the placebo group (64% versus 45%).

The mean duration of asthma was similar across trials and was around 20 years. In MENSA, all patients had experienced at least one exacerbation in the past 12 months, with the majority of patients (about 43%) experiencing two exacerbations. In SIRIUS, 16% of patients had not experienced an exacerbation in the past 12 months, and more than 30% of patients had experienced at least four exacerbations. In MENSA and SIRIUS, a greater proportion of patients in the placebo group had experienced two exacerbations in the past year compared with the mepolizumab group (MENSA, 47% versus 38%; SIRIUS, 21% versus 13%). In MENSA and SIRIUS, patients in the placebo group had a slightly higher pre-bronchodilator and post-bronchodilator FEV_1 at screening than patients in the mepolizumab group. All patients were on high-dose ICS in the past 12 months, and the majority of patients in MENSA (87%) and all patients in SIRIUS were also on an additional controller medication. Approximately 30% of patients in MENSA were on continuous OCS, while all patients in SIRIUS were on high-dose OCS as per inclusion criteria. The majority of patients (> 85%) were on an ICS + LABA combination therapy, with fluticasone propionate plus salmeterol being the most common combination.

In MENSA, approximately 12% of patients had a treatment history with omalizumab, and in SIRIUS, 33% of patients had previously taken omalizumab. The majority of these patients had stopped treatment with omalizumab due to lack of efficacy. For enrolment, patients were to have stopped treatment with omalizumab at least 130 days before visit 1.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Characteristics	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Demographics				
Age (years), mean (SD)	51.2 (14.6)	49.2 (14.3)	49.8 (14.1)	49.9 (10.3)
Age 12 to 17 years, n (%)	7 (4)	9 (5)	2 (3)	0
Age ≥ 18 years, n (%)	187 (96)	182 (95)	67 (97)	66 (100)
Female, n (%)	116 (60)	107 (56)	44 (64)	30 (45)
White, n (%)	152 (78)	148 (77)	67 (97)	61 (92)

Characteristics	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Asian, n (%)	34 (18)	38 (20)	1 (1)	2 (3)
Asthma duration (years), mean (SD)	20.5 (12.9)	19.5 (14.6)	17.4 (11.8)	20.1 (14.4)
Number of Exacerbations in Past 12 Months, n (%)				
0	0	0	12 (17)	10 (15)
1	0	1 (< 1)	11 (16)	11 (17)
2	74 (38)	89 (47)	9 (13)	14 (21)
3	48 (25)	46 (24)	9 (13)	11 (17)
4	28 (14)	22 (12)	–	–
≥ 4	–	–	28 (41)	20 (30)
≥ 5	44 (23)	33 (17)	–	–
Asthma Disease Characteristics in Past 12 Months, n (%)				
High-dose ICS	194 (100)	191 (100)	69 (100)	66 (100)
Controller medication[a]	170 (88)	166 (87)	69 (100)	66 (100)
SABA usage	118 (61)	115 (60)	52 (75)	49 (74)
Oral steroid bursts	101 (52)	87 (46)	39 (57)	29 (44)
Continuous OCS	58 (30)	59 (31)	69 (100)[b]	66 (100)[b]
Eosinophil Inclusion Criteria, n (%)				
≥300 cells/mcL in past 12 months	146 (75)	121 (63)	50 (72)	42 (64)
≥150 cells/mcL at screening	155 (80)	167 (87)	61 (88)	60 (91)
Lung Function at Screening				
Pre-bronchodilator FEV_1 (mL), mean (SD)	1,635.6 (626.9)	1,726.3 (557.7)	1,853.6 (665.1)	1,936.5 (836.3)
% FEV_1 predicted normal, mean (SD)	56.1 (16.1)	57.8 (14.9)	58.4 (17.9)	55.6 (18.3)
Post-bronchodilator FEV_1 (mL), mean (SD)	2,041.7 (735.1)	2,158.9 (632.0)	2,268.3 (730.2)	2,347.0 (946.0)
% FEV_1 predicted normal, mean (SD)	69.9 (17.9)	72.3 (17.3)	71.8 (19.9)	67.6 (20.5)
Reversibility (%), mean (SD)	28.7 (26.6)	27.2 (20.3)	24.9 (19.3)	23.7 (18.6)
Reversibility (mL), mean (SD)	408.7 (307.2)	429.0 (267.8)	414.6 (269.2)	410.5 (315.3)
Previous Use of Omalizumab				
Previously used, n (%)	25 (13)	21 (11)	23 (33)	22 (33)
Every 2 weeks	15 (8)	10 (5)	15 (22)	10 (15)
Monthly	10 (5)	10 (5)	8 (12)	12 (18)
Previously failed, n (%)	22 (11)	19 (10)	23 (33)	22 (33)
Cost	2 (1)	1 (0.5)	1 (1)	1 (2)
Inconvenience	1 (0.5)	0	0	2 (3)
Lack of efficacy	16 (8)	13 (7)	20 (29)	17 (26)
Side effects	1 (0.5)	3 (2)	2 (3)	2 (3)
Duration (months), mean (SD)	21.4 (20.9)	11.0 (9.5)	11.2 (12.9)	19.8 (19.8)

FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LABA = long-acting beta agonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroids; SABA = short-acting beta agonist; SC = subcutaneous; SD = standard deviation.
[a] Controller medication in addition to high-dose ICS (e.g., LABA, LTRA, theophylline).
[b] All patients received high-dose OCS in the last 12 months.
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

3.2.3 Interventions

In MENSA and SIRIUS, patients were randomized 1:1 to receive mepolizumab 100 mg SC once every four weeks or placebo (0.9% sodium chloride solution). Mepolizumab was available as a lyophilized powder for reconstitution with sterile water, and a topical anesthetic was permitted at the injection site to minimize discomfort as needed. In MENSA, mepolizumab 75 mg IV was also administered as a treatment in a double dummy fashion, where all treatment groups received both SC and IV injections, one of which was a placebo injection in the mepolizumab groups. As the IV formulation of mepolizumab is not approved by Health Canada, only results for the SC formulation are presented in this review.

All concomitant medications taken during the study were recorded, and the dose of OCS taken was also recorded, with dose changes noted. Additional asthma medications such as theophyllines and leukotriene receptor antagonists were permitted if they had been taken regularly in the three months before randomization. Maintenance OCS were permitted. Continuous positive airway pressure (CPAP) for the management of obstructive sleep apnea was also permitted if initiated before screening. Omalizumab was not permitted during the study, and patients required a 130-day washout time before screening.

Salbutamol/albuterol metered-dose inhalers were dispensed at visit 1 to be used as needed for the treatment of asthma symptoms.

3.2.4 Outcomes

a) Asthma Exacerbations

In the trials, an asthma exacerbation was defined as worsening of asthma symptoms that require either treatment with systemic corticosteroids for greater than or equal to three days, hospitalization, or an emergency department visit. A clinically significant exacerbation included the subset of all exacerbations that met the additional criterion of using objective data from the patient's eDiary or from direct communication between site staff and the investigator in the absence of eDiary data (and not from a third-party committee). The verification process was overseen by sponsor clinical staff to ensure consistency. Exacerbations treated with courses of corticosteroids separated by less than seven days were treated as a continuation of the same exacerbation. The primary end point in MENSA was the frequency of clinically significant asthma exacerbations, while secondary end points also included the frequency of exacerbations requiring hospitalization or emergency department visits and the frequency of exacerbations requiring hospitalization. In MENSA, these were evaluated as exploratory end points. A review of the literature did not reveal any evidence of a minimal clinically important difference (MCID).

b) Oral Corticosteroid Use

In SIRIUS, the primary end point was the percentage reduction of OCS dose during weeks 20 to 24 compared with baseline dose while maintaining asthma control. OCS dose adjustments during the reduction phase of the study were based on asthma symptom data collected through the patient's eDiary, the patient's history of clinically significant exacerbation, and the presence of adrenal insufficiency. Patients were to record their daily dose of OCS in their eDiary. A reduction was not performed if the patient had the following characteristics: mean morning PEF < 80% of baseline stability limit; mean asthma-related nighttime awakenings > 50% increase over baseline period (per night) and > 150% of baseline mean; rescue medication use requiring ≥ 4 puffs/day above the mean baseline value for two consecutive days in the prior week, or ≥ 12 puffs/day on any one day in the prior week; change in ACQ-5 score ≥ 0.5 from prior month; symptoms of adrenal insufficiency. OCS dose reduction was performed every four weeks using the titration schedule presented in Table 6. Patients on lower doses

of OCS at baseline could be completely weaned from OCS, while patients on OCS doses of ≥ 25 mg/day would not be completely weaned to prevent adrenal crises.

TABLE 6: ORAL CORTICOSTEROID REDUCTION PHASE TITRATION SCHEDULE IN SIRIUS

Time Course	OCS Dose (mg/day)								
Optimized OCS Dose	**35**	**30**	**25**	**20**	**15**	**12.5**	**10.0**	**7.5**	**5.0**
First dose reduction	25.0	20.0	15.0	10.0	10.0	10.0	5.0	5.0	2.5
+ 4 weeks	15.0	10.0	10.0	5.0	5.0	5.0	2.5	2.5	1.25
+ 4 weeks	10.0	5.0	5.0	2.5	2.5	2.5	1.25	1.25	0
+ 4 weeks	5.0	2.5	2.5	1.25	1.25	1.25	0	0	0
+ 4 weeks	2.5	2.5	2.5	0	0	0	0	0	0

OCS = oral corticosteroids.
Source: SIRIUS Clinical Study Report.[2]

c) Pulmonary Function

FEV_1 is the maximal volume of air after a full inspiration that can be forcibly exhaled in one second. It is measured electronically by spirometry. This measure can be converted to a percentage of predicted normal value that is adjusted by height, weight, and race. The percentage of predicted FEV_1 is a commonly reported pulmonary function test and is considered a valid marker for the degree of airway obstruction with asthma.[20] However, although it is widely used in clinical trials to evaluate the effectiveness of asthma treatments, there is little literature on the MCID for FEV_1-based measures. Historically, an MCID of 100 mL has been proposed, although little evidence exists to support this value. However, in a study of 281 adult asthmatic patients, a minimal patient perceivable improvement (MPPI) for FEV_1 was determined by comparing the average baseline FEV_1 scores with patient global ratings of change in asthma. Across all patients, the MPPI for FEV_1 was 230 mL, or 10.38% change from baseline.

In MENSA, the change from baseline in clinic pre-bronchodilator FEV_1 at week 32 was a secondary end point, while in SIRIUS, this measure was analyzed at week 24 as an exploratory end point. FEV_1 assessments were conducted on site at all visits and were performed at the same time of day as measurements performed at visit 2. Patients were to withhold short-acting beta agonist administration for ≥ 6 hours and LABAs for ≥ 12 hours before the clinic visit if possible.

PEF is the peak volume expired, independent of time, during a forced exhalation.[21] Some trialists have used a value of 25 L/min as an MCID for PEF values among patients with asthma;[22,23] however, no research seems to support use of this cut-off point (APPENDIX 5). In a study of 281 adult asthmatic patients, an MPPI for PEF has been reported to be 18.8 L/min, with no differences in MPPI values by gender or age (APPENDIX 5). The mean change from baseline in morning PEF at week 32 (MENSA) and during weeks 20 to 24 (SIRIUS) were analyzed as exploratory end points.

d) Quality of Life

The St. George's Respiratory Questionnaire (SGRQ) is a quality-of-life measure developed to assess impaired health and perceived well-being in patients with chronic airflow limitation. The SGRQ consists of 50 items (with 76 weighted responses) covering three dimensions: symptoms (measuring distress due to respiratory symptoms), activity (measuring the effect of disturbances on mobility and physical activity), and impacts (measuring the psychosocial impact of the disease). Total SGRQ scores range from

0 to 100, with higher values indicating lower health-related quality of life. Among patients with asthma, the generally accepted MCID for a change in total SGRQ from baseline is 4.0 units, and a decrease in score indicates an improvement in health-related quality of life (APPENDIX 5). The mean change from baseline in SGRQ score at week 32 was assessed as a secondary end point in MENSA, while in SIRIUS, this measure was analyzed at week 24 as an exploratory end point.

e) Asthma Symptoms

The Asthma Control Questionnaire (ACQ) is a patient-reported instrument that measures the adequacy of asthma treatment; it consists of seven items, including five items on symptoms (nighttime awakenings, symptom severity upon awakening, activity limitation due to asthma, shortness of breath due to asthma, and wheezing within the past week), one item on rescue bronchodilator use, and one item on FEV_1 per cent of predicted normal.[24] Questions are scored on a 7-point scale, which ranges from 0 (indicating good control) to 6 (poor control). The overall score is the mean of all seven questions, with higher scores indicating poorer control.[24] Patients recall their relevant experiences during the previous seven days. There are three shortened versions of the original seven-item ACQ. These include a five-item measure that includes only the symptoms items (ACQ-5), as well as two six-item variants (ACQ-6a: symptoms plus rescue bronchodilator use; and ACQ-6b: symptoms plus FEV_1 per cent of predicted normal).[25]

The ACQ-5 was used to assess asthma symptoms in both studies. The mean change from baseline in the ACQ-5 score at week 32 (MENSA) and week 24 (SIRIUS) was assessed as an exploratory end point. The estimated MCID for all versions of the ACQ has been reported to be 0.5 (APPENDIX 5).

f) Use of Rescue Medication

Patients were permitted to take salbutamol/albuterol inhalation aerosol as rescue medication for as-needed relief from their asthma symptoms. The use of rescue medication was recorded daily by patients in their eDiary and reviewed by the investigator at each clinic visit. The mean change from baseline in daily salbutamol/albuterol use was evaluated as an exploratory end point in both studies. In addition, the mean change from baseline in nighttime awakenings due to asthma symptoms requiring rescue medication use was also evaluated as an exploratory end point in both studies.

g) Harms

AEs and serious adverse events (SAEs) were collected from the start of study treatment until the follow-up visit or the exit visit for patients who entered the open-label extension. All AEs and SAEs were collected, documented, and reported to the sponsor by the study investigator or site staff. An AE was defined as any untoward medical occurrence in a patient temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This could therefore include any exacerbation of a condition, emergence of a new condition or signs — including abnormal laboratory findings — symptoms, or clinical sequelae of a suspected interaction or overdose of any treatment. SAEs could include any unexpected complications that resulted in death, were considered life-threatening, or resulted in disability or hospitalization. Systemic and injection-site reactions were also reported, and cardiovascular events were reported and adjudicated by a clinical end point committee.

3.2.5 Statistical Analysis

a) Sample Size Calculation

MENSA planned for 180 patients to be randomized to each treatment group in order to have 90% power to detect a 40% decrease in exacerbation rate (seen in previous mepolizumab studies) from 2.4 per annum on placebo (based on data from DREAM) to 1.44 per annum on each of the mepolizumab treatment groups using a two-sided 5% significance level. The calculation assumed that the number of exacerbations per year followed a negative binomial distribution with a dispersion parameter of k = 0.8 (based on data from DREAM). It was assumed that 11% of patients would withdraw prematurely and that these patients would contribute data for an average of 50% of the 32-week double-blind period.

SIRIUS planned for 60 patients to be randomized to each treatment group in order to have 90% power to detect an odds ratio (OR) of 2.9 (based on data from similar corticosteroid-sparing studies in asthma) of an improved OCS dose reduction category with mepolizumab compared with placebo. SIRIUS was also designed to detect an increase of 25% in the proportion of patients achieving ≥ 50% reduction in OCS dose.

b) Statistical Tests

In both studies, the intention-to-treat population was used for all analyses of efficacy and safety outcomes. The per-protocol population was used for supportive analyses for the primary efficacy end points.

Exacerbations: In MENSA and SIRIUS, the frequency of exacerbations over the double-blind treatment period was expressed as exacerbation rate per year. The exacerbation rate was analyzed using a generalized linear model, assuming the number of exacerbations had a negative binomial probability distribution. In MENSA, the model included covariates for treatment, region, baseline maintenance OCS therapy, number of exacerbations in the past year, and baseline disease severity (% predicted FEV_1). In SIRIUS, the model included covariates for treatment, region, duration of OCS use at baseline (< 5 years versus ≥ 5 years), and dose of OCS at baseline. The analysis using a negative binomial model assumes that missing data are missing at random, and further sensitivity analyses were performed using multiple imputation methods based on pattern mixed models. In MENSA, exploratory multivariate modelling was used to investigate baseline variables predictive of the overall number of clinically significant exacerbations (pre-specified subgroup analyses). Time-to-first-exacerbation outcomes were evaluated using Cox proportional hazards models with the same covariates mentioned above.

OCS use: In SIRIUS, the number of patients in each category for percentage reduction of OCS dose at weeks 20 to 24 compared with the baseline dose (primary end point) was analyzed using a proportional odds model with covariates for treatment, region, duration of OCS use at baseline (< 5 years versus ≥ 5 years), and dose of OCS at baseline. An OR for treatment difference and associated 95% confidence limits were presented. A binary logistic regression model was used to analyze the proportion of patients who achieved a reduction of ≥ 50% in daily OCS dose compared with baseline, a reduction of OCS dose to ≤ 5.0 mg, and a total reduction of OCS dose, with the same covariates as the primary end point. The median percentage reduction from baseline in daily OCS dose was analyzed using a Wilcoxon rank-sum test. Patients who withdrew or had missing data were assigned to the lowest efficacy category.

Pulmonary function: Change from baseline in pre-bronchodilator FEV_1 was analyzed using a mixed model for repeated measures adjusting for baseline FEV_1, baseline maintenance OCS therapy, region, number of exacerbations in the past year, and visit, with interaction terms for visit by baseline and visit by

treatment group. Change from baseline in morning PEF was summarized descriptively using eDiary data, with data aggregated over four-week periods.

SGRQ: Change from baseline in SGRQ score was analyzed using an analysis of covariance (ANCOVA) model with baseline SGRQ, baseline maintenance OCS therapy, region, number of exacerbations in the past year, and baseline % predicted FEV_1 as covariates.

ACQ-5: Change from baseline in ACQ-5 score was analyzed using a mixed model for repeated measures model adjusting for covariates of baseline ACQ, baseline maintenance OCS therapy, region, number of exacerbations in the past year, and visit, with interaction terms for visit by baseline and visit by treatment group.

Rescue salbutamol/albuterol use: Daily diary data were aggregated over four-week periods, and mean daily usage (excluding days with missing data) was calculated for each four-week period. Change from baseline for each four-week period was summarized by treatment group.

c) Multiplicity

MENSA was designed to test the superiority of mepolizumab 75 mg IV versus placebo and the superiority of mepolizumab 100 mg SC versus placebo. A step-down closed testing procedure was used to control for multiple statistical testing. Significance was declared if both mepolizumab 75 mg IV versus placebo and mepolizumab 100 mg SC versus placebo demonstrated statistical significance at the unadjusted one-sided 2.5% level, or if at least one of these tests demonstrated statistical significance at the unadjusted one-sided 1.25% level. The hierarchy of end points was defined as follows:

- Rate of clinically significant exacerbations (primary end point)
- Rate of exacerbations requiring hospitalization or emergency department visits
- Rate of exacerbations requiring hospitalization
- Change from baseline in clinic pre-bronchodilator FEV_1 at week 32
- Change from baseline in SGRQ score at week 32

In SIRIUS, no adjustments for multiplicity were made for the secondary end points because they were considered to be sensitivity analyses to the primary end point.

d) Analysis Populations

In the included studies, the following data sets were defined:

Intention-to-Treat: A modified intention-to-treat population was used, which included patients who were randomized and received at least one dose of study medication. The modified intention-to-treat population was used for all analyses of efficacy and safety outcomes.

Per-Protocol: The per-protocol population included all patients in the intention-to-treat population not identified as full protocol deviators with respect to criteria that were considered to impact the primary efficacy analysis. The decision to exclude a patient from the per-protocol population was made before unblinding.

3.3 Patient Disposition

In MENSA, 17% of patients screened did not meet randomization criteria during the run-in period. The majority of these patients did not meet the eosinophilic phenotype criteria. In SIRIUS, 25% of patients

screened did not meet randomization criteria during the run-in period. The majority of these patients did not achieve an optimized OCS dose (17 patients) or failed to meet eosinophilic phenotype criteria (10 patients).

Discontinuations were low and balanced between mepolizumab and placebo groups in both studies (about 5%) and more than 90% of patients who were randomized and treated in the MENSA and SIRIUS trials completed the study and moved on to the open-label extension (Study MEA115661; (APPENDIX 6).

TABLE 7: PATIENT DISPOSITION

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC	Placebo	Mepolizumab 100 mg SC	Placebo
Screened, N	802 (100)		185 (100)	
Run-In, n (%)	720 (90)		182 (98)	
Run-In Failure, n (%)	140 (17)		47 (25)	
Randomization criteria	120 (15)		42 (23)	
Randomized, n (%)	580 (72)		135 (73)	
	194 (24)[a]	193 (24)[a]	69 (37)	66 (36)
Treated, n (%)	**194 (100)**	**191 (100)[b]**	**69 (100)**	**66 (100)**
Discontinued, n (%)	9 (5)	12 (6)	3 (4)	4 (6)
Withdrawal by patient	4 (2)	5 (3)	0	1 (2)
Adverse event	1 (< 1)	4 (2)	3 (4)	3 (5)
Lack of efficacy	2 (1)	1 (< 1)	0	0
Physician decision	0	2 (1)	0	0
Entered Open-Label Extension, n (%)	176 (91)	175 (92)	65 (94)	61 (92)
ITT, n	194 (100)	191 (100)	69 (100)	66 (100)
PP, n	180 (93)	181 (95)	61 (88)	61 (92)
Safety, n	194 (100)	191 (100)	69 (100)	66 (100)

ITT = intention-to-treat; IV = intravenous; PP = per-protocol; SC = subcutaneous.
[a] Numbers for the mepolizumab 75 mg IV group are not presented.
[b] Two patients in the placebo group were randomized in error and did not receive treatment.
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

3.4 Exposure to Study Treatments

The extent of exposure was similar between treatment groups in MENSA and SIRIUS, with most patients receiving all schedule injections and completing the entire length of double-blind treatment (Table 8).

In MENSA and SIRIUS, approximately [redacted] of patients were on a background therapy of an ICS + LABA and a non-LABA controller, while [redacted] of patients were on a background therapy of ICS + LABA alone (Table 9). In SIRIUS, all patients were taking concomitant OCS as per inclusion criteria. The most common ICS + LABA combination was fluticasone propionate plus salmeterol.

TABLE 8: EXTENT OF EXPOSURE

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Number of injections administered, mean (SD)	7.7 (1.3)	7.7 (1.2)	5.8 (0.9)	5.9 (0.6)
All planned injections administered, n (%)	183 (94)	179 (94)	65 (94)	63 (95)
Time on treatment (days), mean (SD)	219.2 (37.5)	219.2 (35.3)	164.5 (25.7)	167.6 (16.4)

SC = subcutaneous; SD = standard deviation.
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

TABLE 9: CONCOMITANT ASTHMA MEDICATIONS TAKEN DURING DOUBLE-BLIND TREATMENT

Concomitant Asthma Medication	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
ICS + LABA alone	[redacted]	[redacted]	[redacted]	[redacted]
ICS + LABA + non-LABA controller	[redacted]	[redacted]	[redacted]	[redacted]
ICS + non-LABA controller	[redacted]	[redacted]	[redacted]	[redacted]

ICS = inhaled corticosteroids; LABA = long-acting beta$_2$ agonist; SC = subcutaneous.
Source: Manufacturer-provided additional information.[26]

3.5 Critical Appraisal

3.5.1 Internal Validity

Small sample sizes in SIRIUS may have led to some imbalance in baseline characteristics between the mepolizumab and placebo groups, particularly in the proportion of females (64% versus 45%). In SIRIUS, randomization was stratified according to duration of OCS use and not by any other variables. However, the clinical expert involved in the review stated that there were no imbalances that were cause for concern in SIRIUS. In both MENSA and SIRIUS, there was a greater proportion of patients who experienced two exacerbations in the past year in the placebo groups compared with the mepolizumab groups. In MENSA, the statistical model included adjustment for baseline exacerbations, while in SIRIUS, this adjustment was not included in the model. In addition, pre-bronchodilator and post-bronchodilator FEV_1 values at screening were slightly higher in the placebo groups than in the mepolizumab groups in both studies, and no adjustments were made for this variable.

It was unclear whether exacerbations were adjudicated by a central committee. It appeared that the site staff examined patient eDiary data and investigator reports to confirm clinically significant exacerbations. As there did not appear to be external adjudication, there is potential for bias. Blinding may have been compromised due to injection-site reactions associated with mepolizumab. However, the incidence of injection-site reactions was low across groups (< 10%).

A testing hierarchy was used to control for multiplicity for secondary end points in MENSA. This is an appropriate strategy, and the manufacturer adhered to their stated hierarchical testing procedure. Outcomes outside of the testing hierarchy need to be interpreted as exploratory. No testing hierarchy was used in SIRIUS, as secondary outcomes were considered to be sensitivity analyses of the primary outcome.

In MENSA, the placebo group also showed improvement in efficacy outcomes, including subjective outcomes such as change from baseline in SGRQ at week 32 (mean change –9.2 [standard deviation (SD)0 16.6]), and objective outcomes such as change from baseline in pre-bronchodilator FEV_1 at week 32 (mean change 70 mL [SD 415]). This may be partly due to an improved adherence to background medication in a clinical trial setting compared with a real-life setting.

3.5.2 External Validity

The included trials had a relatively short duration (32 weeks in MENSA, 24 weeks in SIRIUS) and thus were not designed to assess clinical outcomes such as mortality. The clinical expert consulted for this review noted that it would be better to see a 52-week study to evaluate asthma exacerbations, as exacerbations fluctuate with each season. Hence, the evidence for the benefits of mepolizumab for reducing the incidence of acute asthma exacerbations, as well as evidence of safety, is based on relatively short-term studies; the long-term effects and harms associated with mepolizumab are uncertain. The manufacturer submitted evidence from a 52-week open-label extension study of patients enrolled in MENSA and SIRIUS (MEA115661) (APPENDIX 6); however, the open-label uncontrolled design and select population make it very difficult to assess whether the reductions in exacerbations observed in MENSA and SIRIUS are sustained past 24 to 36 weeks.

According to the clinical expert consulted for this review, blood eosinophil inclusion criteria may not relate as strongly to airway eosinophilia as sputum eosinophil levels, and sputum eosinophil counts are preferred by clinicians for this. However, obtaining sputum eosinophil counts is difficult in the clinical setting and requires considerable expertise and standardization.[27] Peripheral eosinophil counts are easier to obtain, though their positive predictive value for eosinophilic asthma is low.[27]

According to the clinical expert, peripheral eosinophil levels of ≥ 150 cells/mcL alone may not be specific enough to identify patients with SEA and a higher cut-off would be preferred. However, it appears that in this group of patients with uncontrolled asthma while on high-dose ICS and an additional controller, blood eosinophil levels of ≥ 150 cells/mcL may indicate severe asthma with an eosinophilic component. Patients in SIRIUS were also on regular treatment with OCS, indicating a higher severity than patients in MENSA, where only 30% of patients were on regular treatment with OCS. Due to the adverse side effects of OCS, SEA patients who are on regular OCS treatment may have an additional benefit from mepolizumab due to the ability to decrease their OCS dose and associated side effects.

In SIRIUS, the titration schedule for OCS dose reduction was more aggressive than what would be used in clinical practice for patients on a starting dose of 25 mg/day to 30 mg/day, assuming that patients in the study had been taking OCS for a prolonged period. The length of time patients were on OCS before the study was not reported.

Compliance to background asthma therapies was not reported. Patients may have been more compliant to therapies in a clinical trial setting than in a real-life setting, potentially limiting the generalizability of these results. However, the clinical expert noted that patients with this severity of asthma would likely be adherent to their therapies.

Fewer than 5% of patients were between 12 years and 17 years of age in the included trials. Since asthma affects young patients, there is a lack of data on the efficacy of mepolizumab in this age group. Due to the lack of data, the Health Canada indication for mepolizumab SC was restricted to adult patients.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See APPENDIX 4 for detailed efficacy data.

3.6.1 Asthma Exacerbations

The proportion of patients experiencing a clinically significant exacerbation was lower in the mepolizumab group than in the placebo group in both studies (MENSA, 33% versus 55%; SIRIUS, 42% versus 68%) (Table 10). The rate of clinically significant exacerbations was statistically significantly lower in the mepolizumab group than in the placebo group in MENSA over 32 weeks (rate ratio 0.47; 95% CI, 0.35 to 0.64; $P < 0.001$). In SIRIUS, the clinically significant exacerbation rate per year was also lower in the mepolizumab group than in the placebo group over 24 weeks (rate ratio 0.68; 95% CI, 0.47 to 0.99). Mepolizumab also demonstrated a statistically significant reduction in the risk of a first clinically significant exacerbation compared with the placebo group (MENSA, hazard ratio 0.44; 95% CI, 0.32 to 0.60; SIRIUS, hazard ratio 0.49; 95% CI, 0.31 to 0.78).

In MENSA, the rate of exacerbations requiring hospitalization or emergency department visit was statistically significantly lower in the mepolizumab group than in the placebo group (rate ratio 0.39; 95% CI, 0.18 to 0.83; $P = 0.015$). The rate of exacerbations requiring hospitalization was lower in the mepolizumab group than in the placebo group (rate ratio 0.31; 95% CI, 0.11 to 0.91; $P = 0.034$), however this outcome fell below a non-statistically significant parameter in the testing hierarchy (comparison of mepolizumab 75 mg IV to placebo for rate of exacerbations requiring hospitalization or emergency department visits), and results from the statistical test should be considered exploratory. In MENSA, mepolizumab demonstrated a reduction in the risk of a first exacerbation requiring hospitalization or emergency department visit (hazard ratio 0.38; 95% CI, 0.19 to 0.78) and exacerbation requiring hospitalization (hazard ratio 0.30; 95% CI, 0.11 to 0.86) compared with the placebo group.

In SIRIUS, the exacerbation rate, rate ratio, and time to exacerbation were not calculated for exacerbations requiring hospitalization or emergency department visit or exacerbation requiring hospitalization due to an insufficient number of events to perform the analysis.

a) Subgroup Analyses

In MENSA, pre-specified subgroup analyses for the rate of clinically significant exacerbations (primary end point) were performed (Table 21). No tests for interactions between subgroups were performed. Similar relative reductions in exacerbation rate were seen across subgroups based on the number of exacerbations in the past year, though the exacerbation rate was higher in patients with a greater number of exacerbations in the past year.

Patients who were on baseline maintenance OCS therapy had a higher rate of exacerbations than patients who were not on baseline maintenance OCS therapy.

With regard to blood eosinophil level at screening, patients with high eosinophil levels (≥ 500 cells/mcL) had a greater reduction in clinically significant exacerbations with mepolizumab versus placebo (rate ratio 0.21; 95% CI, 0.12 to 0.36) compared with patients with lower eosinophil levels (< 150 cells/mcL)

(rate ratio 0.91; 95% CI, 0.44 to 1.90). Patients with screening blood eosinophil levels of 150 cells/mcL to < 300 cells/mcL and 300 cells/mcL to < 500 cells/mcL showed similar reductions in clinically significant asthma exacerbations with mepolizumab compared with placebo (rate ratio 0.48; 95% CI, 0.27 to 0.86; and rate ratio 0.48; 95% CI, 0.26 to 0.89).

When analyzed by screening blood eosinophil inclusion criteria, patients who had eosinophil levels of ≥ 150 cells/mcL at screening had a reduction in clinically significant exacerbations with mepolizumab versus placebo (rate ratio 0.38; 95% CI, 0.27 to 0.53) compared with patients who did not have eosinophil levels of ≥ 150 cells/mcL (rate ratio 0.91; 95% CI, 0.44 to 1.90). This pattern was not observed for the eosinophil inclusion criterion of ≥ 300 cells/mcL in the past 12 months. Patients who demonstrated eosinophil levels of ≥ 300 cells/mcL only in the past 12 months without ≥ 150 cells/mcL at screening had a reduced reduction in clinically significant exacerbations with mepolizumab versus placebo (rate ratio 0.82; 95% CI, 0.38 to 1.77) compared with patients who demonstrated eosinophil levels of ≥ 150 cells/mcL at screening without ≥ 300 cells/mcL in the past 12 months (rate ratio 0.26; 95% CI, 0.14 to 0.52).

Patients who had a baseline immunoglobulin E concentration of ≤ 30 U/mL did not demonstrate a reduction in clinically significant exacerbations with mepolizumab versus placebo (rate ratio 1.00; 95% CI, 0.47 to 2.10). However, this subgroup was small (24 patients in mepolizumab group, 28 patients in placebo group). Patients with baseline immunoglobulin E concentrations of > 30 U/mL demonstrated comparable reductions in clinically significant exacerbations with mepolizumab versus placebo as the primary analysis.

Patients who had previous use of omalizumab demonstrated similar reductions in clinically significant exacerbations with mepolizumab versus placebo (rate ratio 0.59; 95% CI, 0.28 to 1.26) compared with patients with no previous use of omalizumab (rate ratio 0.46; 95% CI, 0.33 to 0.63). Few patients in MENSA had received previous treatment with omalizumab (25 patients in mepolizumab group, 21 patients in placebo group).

No subgroup analyses were performed for baseline asthma control medication, use of rescue medications, or diagnosis of allergic asthma.

TABLE 10: ASTHMA EXACERBATIONS IN MENSA AND SIRIUS

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Clinically Significant Exacerbations				
Number of patients, n (%)	64 (33)	105 (55)	29 (42)	45 (68)
Number of exacerbations	116	216	47	68
0	130 (67)	86 (45)	40 (58)	21 (32)
1	41 (21)	51 (27)	16 (23)	28 (42)
2	11 (6)	28 (15)	10 (14)	11 (17)
3	6 (3)	12 (6)	1 (1)	6 (9)
4	1 (< 1)	5 (3)	2 (3)	0
≥ 5	5 (3)	9 (5)	0	0
Exacerbation rate/year	0.83	1.74	1.44	2.12

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Rate ratio (95% CI), *P* value[a]	0.47 (0.35 to 0.64), < 0.001		0.68 (0.47 to 0.99)	
Probability of an exacerbation by end of DB period, % (95% CI)	32.8 (26.6 to 40.0)	56.4 (49.4 to 63.7)	43.7 (32.7 to 56.4)	69.3 (57.9 to 80.1)
Time to exacerbation, HR (95% CI)[b]	0.44 (0.32 to 0.60)		0.49 (0.31 to 0.78)	
Exacerbations Requiring Hospitalization or ED Visit				
Number of patients, n (%)	11 (6)	24 (13)	3 (4)	7 (11)
Number of exacerbations	20	33	3	9
Exacerbation rate/year	0.08	0.20	–[c]	–
Rate ratio (95% CI), *P* value[a]	0.39 (0.18 to 0.83), *P* = 0.015		–	
Probability of an exacerbation by end of DB period, % (95% CI)	5.9 (3.3 to 10.3)	12.9 (8.9 to 18.7)	4.5 (1.5 to 13.4)	10.7 (5.3 to 21.2)
Time to exacerbation, HR (95% CI)[b]	0.38 (0.19 to 0.78)		0.39 (0.10 to 1.50)	
Exacerbations Requiring Hospitalization				
Number of patients, n (%)	5 (3)	13 (7)	0	7 (11)
Number of exacerbations	9	18	0	8
Exacerbation rate/year	0.03	0.10	–[c]	–
Rate ratio (95% CI), *P* value[a]	0.31 (0.11 to 0.91), *P* = 0.034[d]		–	
Probability of an exacerbation by end of DB period, % (95% CI)	1.6 (0.5 to 4.8)	5.3 (2.9 to 9.7)	0	10.8 (5.3 to 21.3)
Time to exacerbation, HR (95% CI)[b]	0.30 (0.11 to 0.86)		–	

CI = confidence interval; DB = double blind; ED = emergency department; HR = hazard ratio; SC = subcutaneous.
[a] Generalized linear model with covariates for treatment, region, baseline maintenance OCS therapy, number of exacerbations in the past year, and baseline disease severity (% predicted FEV_1) in SIRIUS; covariates for treatment, region, duration of OCS use at baseline (< 5 years versus ≥ 5 years, and dose of OCS at baseline in MENSA.
[b] Cox proportional hazards model with same covariates as mentioned in footnote "a".
[c] Insufficient events to perform analysis.
[d] Descriptive as outcome fell below a non-statistically significant parameter in the testing hierarchy.
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

3.6.2 Use of Oral Corticosteroids

The use of OCS to treat clinically significant exacerbations was an exploratory end point in both MENSA and SIRIUS and was reported descriptively (Table 11). Generally, the number of days of OCS treatment per exacerbation and the prednisone equivalent dose per exacerbation were similar between treatment groups in both studies. However, there was a greater number of clinically significant exacerbations treated with OCS in the placebo group compared with the mepolizumab group in both studies (MENSA, 208 versus 105; SIRIUS, 66 versus 47), which amounted to a greater number of days of OCS use associated with a clinically significant exacerbation (MENSA, 2,037 days versus 1,102 days; SIRIUS, 727 days versus 511 days) and total prednisone equivalent dose (MENSA, 66,757 mg versus 41,008 mg;

SIRIUS, 19,668 mg versus 16,618 mg) administered in the placebo group compared with the mepolizumab group.

TABLE 11: ORAL CORTICOSTEROID USE FOR CLINICALLY SIGNIFICANT EXACERBATIONS IN MENSA AND SIRIUS

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Number of days of OCS use associated with a clinically significant exacerbation	1,102	2,037	511	727
Total prednisone equivalent dose (mg)	41,008	66,757	16,618	19,668
Number of clinically significant exacerbations	116	216	47	68
Number of clinically significant exacerbations treated with OCS	105	208	47	66
Days of OCS treatment per exacerbation treated with OCS, mean (SD)	11.1 (12.4)	10.4 (8.7)	10.8 (8.2)	11.5 (12.9)
Days of OCS treatment per exacerbation treated with OCS, median (range)	7.0 (3 to 64)	8.0 (2 to 55)	8.5 (2 to 35)	8.0 (4 to 83)
Prednisone equivalent dose per exacerbation (mg), mean (SD)	391.0 (664.6)	360.3 (531.7)	317.7 (289.9)	302.2 (275.9)
Prednisone equivalent dose per exacerbation (mg), median (range)	225.0 (40 to 4,675)	226.7 (15 to 4,628)	240.0 (10 to 1,408)	237.5 (70 to 1,610)

OCS = oral corticosteroid; SC = subcutaneous; SD = standard deviation.
Source: MENSA Clinical Study Report.[1]

The percentage reduction from baseline in OCS dose during weeks 20 to 24 was the primary end point in SIRIUS (Table 12). A greater proportion of patients in the mepolizumab group achieved a 90% to 100% reduction from baseline OCS dose compared with the placebo group (23% versus 11%) and a 75% to < 90% reduction (17% versus 8%). However, the highest proportion of patients in both groups achieved no reduction, had a lack of asthma control, or withdrew from treatment (36% versus 56%). The odds ratio of mepolizumab to placebo of achieving a percentage reduction from baseline in OCS dose was statistically significant (OR 2.39; 95% CI, 1.25 to 4.56; *P* = 0.008).

Secondary end points for SIRIUS were considered to be sensitivity analyses of the primary end point. A statistically significantly greater proportion of patients achieved a ≥ 50% reduction in daily OCS dose in the mepolizumab group compared with the placebo group (OR 2.26; 95% CI, 1.10 to 4.65; *P* = 0.027). A statistically significantly greater proportion of patients achieved a reduction in daily OCS dose to ≤ 5 mg in the mepolizumab group compared with the placebo group (OR 2.45; 95% CI, 1.12 to 5.37; *P* = 0.025). More patients in the mepolizumab group achieved a total reduction in OCS dose compared with the placebo group, but this difference was not statistically significant (OR 1.67; 95% CI, 0.49 to 5.75; *P* = 0.414). There was a statistically significant median percentage reduction from baseline in daily OCS dose in the mepolizumab group compared with the placebo group (median difference –30.0; 95% CI, −66.7 to 0.0; *P* = 0.007).

a) Subgroup Analyses

In SIRIUS, pre-specified subgroup analyses for the percentage reduction from baseline in OCS dose (primary end point) were performed (Table 22). When analyzed by subgroups based on baseline OCS dose, patients with a baseline dose of 5 mg/day to < 10 mg/day had greater odds of achieving a reduction from baseline in OCS dose with mepolizumab than with placebo (OR 3.56; 95% CI, 0.97 to 13.11), though the confidence interval crossed 1. Patients with a baseline dose of ≥ 15 mg/day had greater odds of achieving a reduction from baseline in OCS dose with mepolizumab than with placebo (OR 6.25; 95% CI, 1.67 to 23.38). For patients with a baseline dose of 10 mg/day to < 15 mg/day, there did not appear to be a difference in odds of achieving a reduction from baseline in OCS dose with mepolizumab compared to placebo (OR 1.07; 95% CI, 0.37 to 3.05). However, sample sizes for all subgroups were small.

When analyzed by baseline blood eosinophil levels, patients with baseline levels of < 150 cells/mcL had greater odds of achieving a reduction from baseline in OCS dose with mepolizumab than with placebo (OR 6.87; 95% CI, 1.53 to 30.88). Patients with baseline levels of 300 cells/mcL to < 500 cells/mcL (OR 3.64; 95% CI, 0.69 to 19.24) and 150 cells/mcL to < 300 cells/mcL (OR 2.03; 95% CI, 0.53 to 7.75) appeared to have greater odds of achieving a reduction from baseline in OCS dose with mepolizumab than with placebo, though both confidence intervals crossed 1. For patients with baseline levels of ≥ 500 cells/mcL, there did not appear to be a difference in odds of achieving a reduction from baseline in OCS dose with mepolizumab compared to placebo (OR 1.01; 95% CI, 0.31 to 3.31).

When analyzed by screening blood eosinophil inclusion criteria, patients who met criteria for ≥ 300 cells/mcL in the past 12 months had greater odds of achieving a reduction from baseline in OCS dose with mepolizumab than with placebo (OR 4.35; 95% CI, 1.86 to 10.17), while patients who did not have eosinophil levels of ≥ 300 cells/mcL in the past 12 months did not appear to have a difference in odds of achieving a reduction from baseline in OCS dose with mepolizumab than with placebo (OR 1.16; 95% CI, 0.37 to 3.64). Patients who did not meet criteria for ≥ 150 cells/mcL at screening had greater odds of achieving a reduction from baseline in OCS dose with mepolizumab than placebo (OR 13.29; 95% CI, 0.97 to 188.50), though confidence intervals were very wide due to the low number of patients per treatment group (< 10). Patients who met criteria for ≥ 150 cells/mcL at screening had slightly greater odds of achieving a reduction from baseline in OCS dose with mepolizumab than with placebo (OR 1.92; 95% CI, 0.97 to 3.81), but the confidence interval crossed 1.

TABLE 12: REDUCTION FROM BASELINE IN ORAL CORTICOSTEROID DOSE DURING WEEKS 20 TO 24 IN SIRIUS

	SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
% Reduction From Baseline in OCS Dose, n (%) — Primary End Point		
90% to 100%	16 (23)	7 (11)
75% to < 90%	12 (17)	5 (8)
50% to < 75%	9 (13)	10 (15)
> 0% to < 50%	7 (10)	7 (11)
No reduction, lack of asthma control, or withdrawal	25 (36)	37 (56)
OR (95% CI), *P* value[a]	2.39 (1.25 to 4.56) *P* = 0.008	
≥ 50% Reduction in Daily OCS Dose, n (%) — Secondary End Point		
50% to 100%	37 (54)	22 (33)
< 50%, no reduction, lack of asthma control, or withdrawal	32 (46)	44 (67)

	SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
OR (95% CI), *P* value[a]	2.26 (1.10 to 4.65) *P* = 0.027	
Reduction in Daily OCS Dose to ≤ 5 mg, n (%) — Secondary End Point		
50% to 100%	37 (54)	21 (32)
< 50%, no reduction, lack of asthma control, or withdrawal	32 (46)	45 (68)
OR (95% CI), *P* value[a]	2.45 (1.12 to 5.37) *P* = 0.025	
Total Reduction in OCS Dose, n (%) — Secondary End Point		
100% reduction (0 mg)	10 (14)	5 (8)
OCS taken, lack of asthma control, or withdrawal	59 (86)	61 (92)
OR (95% CI), *P* value[a]	1.67 (0.49 to 5.75) *P* = 0.414	
Median Percentage Reduction in Daily OCS Dose (%) — Secondary End Point		
Median (95% CI)	50.0 (20.0 to 75.0)	0.0 (–20.0 to 33.3)
Median difference (95% CI), *P* value[b]	–30.0 (–66.7 to 0.0) *P* = 0.007	

CI = confidence interval; OCS = oral corticosteroid; OR = odds ratio; SC = subcutaneous.
[a] Binary logistic regression with covariates for treatment group, region, duration of OCS use at baseline (< 5 years versus ≥ 5 years), and baseline OCS dose.
[b] Median difference and CI derived using Hodges-Lehman estimation; *P* value derived using the Wilcoxon rank-sum test; missing data imputed using the minimum percentage reduction in OCS.
Source: SIRIUS Clinical Study Report.[2]

3.6.3 Pulmonary Function

a) Pre-bronchodilator FEV_1

In MENSA, both the mepolizumab group and the placebo group showed improvement from baseline in pre-bronchodilator FEV_1 at week 32 (least squares mean change from baseline 183 mL versus 86 mL) (Table 13). In MENSA, the mean change from baseline in pre-bronchodilator FEV_1 at week 32 was statistically significantly greater in the mepolizumab group than in the placebo group (mean difference 98 mL; 95% CI, 11 to 184; *P* = 0.028). Although this was a secondary end point that was part of a testing hierarchy, statistical results were descriptive as this outcome fell below a non-statistically significant parameter.

In SIRIUS, the mean difference between mepolizumab and placebo for the change from baseline in pre-bronchodilator FEV_1 at week 24 was 114 mL (95% CI, –42 to 271).

b) Morning Peak Expiratory Flow

In MENSA, the mean change from baseline in morning PEF during the last four weeks of the double-blind period was 29.5 (SD 69.0) L/min in the mepolizumab group and 1.8 (SD 58.9) L/min in the placebo group. In SIRIUS, the mean change from baseline in morning PEF during the last four weeks of the double-blind period was 19.1 (SD 56.2) L/min in the mepolizumab group and 4.1 (SD 47.0) L/min in the placebo group. Results were presented descriptively with no statistical testing (Table 14).

TABLE 13: CHANGE FROM BASELINE IN PRE-BRONCHODILATOR AND POST-BRONCHODILATOR FEV_1 AT END OF DOUBLE-BLIND PERIOD IN MENSA (WEEK 32) AND SIRIUS (WEEK 24)

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Pre-bronchodilator FEV_1, mL				
Baseline mean (SD)	1,730 (659.2)	1,860 (630.8)	1,897 (660.2)	2,005 (822.3)
n at end of DB period	185	179	66	62
Mean at end of DB period (SD)	1,942 (730.8)	1,940 (612.6)	2,034 (680.9)	2,009 (826.2)
Mean change from baseline (SD)	204 (397.9)	70 (414.9)	121 (483.5)	–21 (464.2)
LS mean at end of DB period (SE)	2,005 (31.1)	1,907 (31.4)	2,070 (55.1)	1,955 (56.5)
LS mean change at end of DB period (SE)	183 (31.1)	86 (31.4)	111 (55.1)	–4 (56.5)
Difference (95% CI), *P* value[a]	98 (11 to 184) *P* = 0.028[b]		114 (–42 to 271)	
Post-bronchodilator FEV_1, mL				
Baseline mean (SD)	2,024 (709.7)	2,153 (638.0)	2,238 (726.8)	2,381 (936.3)
n at end of DB period	172	161	60	58
Mean at end of DB period (SD)	2,225 (768.8)	2,187 (663.9)	2,379 (755.9)	2,402 (840.9)
Mean change from baseline (SD)	184 (396.4)	21 (409.9)	108 (358.8)	–45 (433.2)
LS mean at end of DB period (SE)	2,289 (33.3)	2,151 (34.4)	2,454 (47.8)	2,325 (48.7)
LS mean change at end of DB period (SE)	167 (33.3)	30 (34.4)	96 (47.8)	–32 (48.7)
Difference (95% CI)	138 (43 to 232)		128 (–8 to 264)	

CI = confidence interval; DB = double-blind; FEV_1 = forced expiratory volume at 1 second; LS = least squares; MMRM = mixed model for repeated measures; SC = subcutaneous; SD = standard deviation; SE = standard error.
[a] MMRM with covariates for baseline FEV_1, baseline maintenance OCS therapy, region, number of exacerbations in the past year, and visit, with interaction terms for visit by baseline and visit by treatment group.
[b] Descriptive as outcome fell below a non-statistically significant parameter in the testing hierarchy.
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

TABLE 14: CHANGE FROM BASELINE IN MORNING PEAK EXPIRATORY FLOW AT END OF DOUBLE-BLIND PERIOD IN MENSA (WEEKS 29 TO 32) AND SIRIUS (WEEKS 21 TO 24)

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Morning PEF, L/min				
Baseline mean (SD)	255.3 (107.6)	277.0 (105.5)	284.7 (124.8)	311.9 (152.3)
n at end of DB period	183	175	66	63
Mean at end of DB period (SD)[a]	286.4 (115.3)	277.3 (110.4)	306.0 (128.7)	316.7 (149.1)
Mean change from baseline (SD)	29.5 (69.0)	1.8 (58.9)	19.1 (56.2)	4.1 (47.0)

DB = double-blind; PEF = peak expiratory flow; SC = subcutaneous; SD = standard deviation.
[a] Information was collected on a daily basis from the eDiary and averaged over four-week periods.
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

3.6.4 Quality of Life

The SGRQ was used to assess quality of life in MENSA and SIRIUS. Higher scores are indicative of greater impairment, and a change from baseline of four units is considered clinically meaningful (APPENDIX 5). In MENSA, baseline mean SGRQ total scores were similar between mepolizumab and placebo groups (47.9 versus 46.9) (Table 15). At week 32, there was a statistically significantly greater improvement in SGRQ total score in the mepolizumab group compared with the placebo group (mean difference –7.0; 95% CI, –10.2 to –3.8; $P < 0.001$). Although this end point was part of a testing hierarchy, it fell below a non-statistically significant higher-order test in the hierarchy, and results are merely exploratory.

In SIRIUS, the baseline mean SGRQ total score was higher in the mepolizumab group compared with the placebo group (49.6 versus 45.0). At week 24, there was a greater improvement in SGRQ total score in the mepolizumab group compared with the placebo group (mean difference –5.8; 95% CI, –10.6 to −1.0). This was an exploratory outcome.

In both studies, a greater proportion of patients in the mepolizumab group achieved a ≥ 4-point improvement in SGRQ total score at the end of the double-blind period compared with baseline (MENSA, 71% versus 55%; SIRIUS, 58% versus 41%).

TABLE 15: CHANGE FROM BASELINE IN SGRQ TOTAL SCORE AT END OF DOUBLE-BLIND PERIOD IN MENSA (WEEK 32) AND SIRIUS (WEEK 24)

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab (n = 194)	Placebo (n = 191)	Mepolizumab (n = 69)	Placebo (n = 66)
SGRQ Total Score				
n	193	190	69	66
Baseline mean (SD)	47.9 (19.5)	46.9 (19.8)	49.6 (17.8)	45.0 (18.4)
n at end of DB period	185	178	65	61
Mean at end of DB period (SD)	31.5 (20.5)	38.0 (20.0)	40.6 (20.6)	42.1 (19.3)
Mean change from baseline (SD)	–16.3 (17.0)	–9.2 (16.6)	–9.4 (15.7)	–2.4 (11.2)
LS mean (SE)	30.7 (1.1)	37.7 (1.2)	38.5 (1.7)	44.3 (1.7)
LS mean change (SE)	–16.0 (1.1)	–9.0 (1.2)	–8.8 (1.7)	–3.1 (1.7)
Difference (95% CI), *P* value[a]	–7.0 (–10.2 to –3.8) $P < 0.001$[b]		–5.8 (–10.6 to −1.0)	
Cumulative proportion of patients with ≥ 4 point improvement, n (%)	137 (71)	105 (55)	40 (58)	27 (41)

ANCOVA = analysis of covariance; CI = confidence interval; DB = double blind; FEV_1 = forced expiratory volume in 1 second; LS = least squares; OCS = oral corticosteroid; SD = standard deviation; SE = standard error; SGRQ = St. George's Respiratory Questionnaire.

[a] ANCOVA model with covariates for baseline SGRQ, baseline maintenance OCS therapy, region, number of exacerbations in the past year, and baseline % predicted FEV_1.

[b] Descriptive as outcome fell below a non-statistically significant parameter in the testing hierarchy.

Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

3.6.5 Days of Missed School or Work

Information on days off school was reported by approximately 30% of patients across both studies. In MENSA, the mean number of days off school due to asthma symptoms was similar between the mepolizumab and placebo groups (1.0 versus 1.3) (Table 16). In SIRIUS, the placebo group had a lower

mean number of days off school due to asthma symptoms than did the mepolizumab group (0.5 versus 1.2), but sample sizes were low.

Information on days off work was reported by approximately 71% of patients across both studies. In MENSA, the mean number of days off work due to asthma symptoms was similar between the mepolizumab and placebo groups (3.3 versus 3.1). In SIRIUS, the mean number of days off work due to asthma symptoms was higher in the placebo group than in the mepolizumab group (5.7 versus 2.5).

TABLE 16: DAYS OFF SCHOOL AND WORK DUE TO ASTHMA SYMPTOMS IN MENSA AND SIRIUS

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Days Off School Due to Asthma Symptoms				
n (%)	58 (30)	59 (31)	24 (35)	14 (21)
Total number of days	59	78	28	7
Mean (SD)	1.0 (5.1)	1.3 (3.4)	1.2 (3.7)	0.5 (1.2)
Median (range)	0 (0 to 37)	0 (0 to 17)	0 (0 to 16)	0 (0 to 4)
Days Off Work Due to Asthma Symptoms				
n (%)	137 (71)	136 (71)	51 (74)	47 (71)
Total number of days	457	426	128	270
Mean (SD)	3.3 (13.4)	3.1 (9.8)	2.5 (9.4)	5.7 (16.7)
Median (range)	0 (0 to 98)	0 (0 to 93)	0 (0 to 65)	0 (0 to 90)

SC = subcutaneous; SD = standard deviation.
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

3.6.6 Symptom Reduction

In MENSA, patients had similar mean baseline ACQ-5 total scores across the mepolizumab and placebo groups (2.26 versus 2.28) (Table 17). There was a greater improvement from baseline in ACQ-5 total score at week 32 in the mepolizumab group compared with the placebo group (mean difference –0.44; 95% CI, –0.63 to –0.25).

In SIRIUS, patients had a slightly higher mean baseline ACQ-5 total score in the mepolizumab group compared with the placebo group (2.15 versus 1.99). There was a greater improvement from baseline in ACQ-5 total score at week 24 in the mepolizumab group than in the placebo group (mean difference — 0.52; 95% CI, –0.87 to –0.17).

Change from baseline in ACQ-5 total score was an exploratory outcome in both studies.

TABLE 17: CHANGE FROM BASELINE IN ACQ-5 TOTAL SCORE AT END OF DOUBLE-BLIND PERIOD IN MENSA (WEEK 32) AND SIRIUS (WEEK 24)

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
ACQ-5 Total Score				
n	191	186	69	66
Baseline mean (SD)	2.26 (1.27)	2.28 (1.19)	2.15 (1.27)	1.99 (1.18)
n at end of DB period	176	175	58	53

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Mean at end of DB period (SD)	1.23 (1.10)	1.72 (1.13)	1.48 (1.27)	1.97 (1.29)
Mean change from baseline (SD)	–0.93 (1.15)	–0.55 (0.99)	–0.69 (1.09)	–0.02 (1.28)
LS mean (SE)	1.26 (0.07)	1.70 (0.07)	1.46 (0.13)	1.98 (0.13)
LS mean change (SE)	–0.94 (0.07)	–0.50 (0.07)	–0.61 (0.13)	–0.09 (0.13)
Difference (95% CI)[a]	–0.44 (–0.63 to –0.25)		–0.52 (–0.87 to –0.17)	

ACQ-5 = Asthma Control Questionnaire 5; CI = confidence interval; DB = double blind; LS = least squares; MMRM = mixed model for repeated measures; SC = subcutaneous; SD = standard deviation; SE = standard error.
[a] MMRM with covariates for baseline ACQ-5, baseline maintenance OCS therapy, region, number of exacerbations in the past year, and visit, with interaction terms for visit by baseline and visit by treatment group.
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

3.6.7 Asthma Symptom–Free Days and Nights

The change in the number of asthma symptom–free days and nights was not assessed in the included trials.

3.6.8 Nocturnal Awakenings

Baseline mean nighttime awakenings due to asthma symptoms requiring rescue medication were balanced between mepolizumab and placebo groups across both studies (MENSA, 0.8 versus 0.7; SIRIUS, 0.7 versus 0.5) (Table 18). The mean change from baseline in nighttime awakenings during the four weeks at the end of study was similar between mepolizumab and placebo groups across both studies (MENSA, –0.5 versus –0.3; SIRIUS, –0.3 versus –0.3), with small decreases in both groups.

TABLE 18: CHANGE FROM BASELINE IN NIGHTTIME AWAKENINGS REQUIRING RESCUE MEDICATION USE AT END OF DOUBLE-BLIND PERIOD IN MENSA (WEEKS 28 TO 32) AND SIRIUS (WEEKS 21 TO 24)

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Nighttime Awakenings Due to Asthma Symptoms Requiring Rescue Medication				
Baseline mean (SD)	0.8 (1.1)	0.7 (1.1)	0.7 (1.0)	0.5 (0.7)
n at end of DB period	183	175	66	63
Mean at end of DB period (SD)[a]	0.3 (0.6)	0.3 (0.8)	0.4 (1.1)	0.2 (0.4)
Mean change from baseline (SD)	–0.5 (0.9)	–0.3 (0.8)	–0.3 (0.9)	–0.3 (0.6)

DB = double blind; SC = subcutaneous; SD = standard deviation.
[a] Information was collected on a daily basis from the eDiary and averaged over four-week periods.
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

3.6.9 Reduction in Use of Inhaled Corticosteroids

The reduction in use of ICS was not assessed in the included trials.

3.6.10 Use of Rescue Medication

Baseline daily rescue medication use was generally balanced between mepolizumab and placebo groups across both studies, with higher use in SIRIUS due to the severity of patients who were enrolled

(MENSA, 1.9 occasions/day versus 1.7 occasions/day; SIRIUS, 3.0 occasions/day versus 3.6 occasions/day) (Table 19). The mean change from baseline in daily rescue medication use during the four weeks at the end of study was similar between mepolizumab and placebo groups across both studies (MENSA, –0.7 occasions/day versus –0.5 occasions/day; SIRIUS, −0.8 occasions/day versus –0.8 occasions/day)

TABLE 19: CHANGE FROM BASELINE IN DAILY RESCUE MEDICATION USE AT END OF DOUBLE-BLIND PERIOD IN MENSA (WEEKS 28 TO 32) AND SIRIUS (WEEKS 21 TO 24)

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Daily Rescue Medication Use (Occasions/Day)				
Baseline mean (SD)	1.9 (2.3)	1.7 (2.0)	3.0 (3.0)	3.6 (4.8)
n at end of DB period	183	175	66	63
Mean at end of DB period (SD)[a]	1.2 (2.6)	1.2 (2.0)	2.4 (3.6)	3.0 (4.4)
Mean change from baseline (SD)	–0.7 (2.5)	–0.5 (1.6)	–0.8 (2.5)	–0.8 (2.1)

DB = double blind; SC = subcutaneous; SD = standard deviation.
[a] Information was collected on a daily basis from the eDiary and averaged over four-week periods.
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

3.6.11 Mortality

In MENSA, one patient in the placebo group died due to a traffic accident after having received eight doses of the investigational product. In SIRIUS, one patient in the placebo group died from severe sepsis and subsequent GI bleeding and aspiration after hospitalization due to a severe asthma exacerbation after having received six doses of the investigational product.

3.7 Harms

Only those harms identified in the review protocol are reported below. See APPENDIX 4 for detailed harms data.

3.7.1 Adverse Events

In MENSA, a total of 78% of patients in the mepolizumab group and 83% of patients in the placebo group reported an AE during the 32-week double-blind treatment period. In SIRIUS, a total of 83% of patients in the mepolizumab group and 92% of patients in the placebo group reported an AE during the 24-week double-blind OCS dose reduction treatment period. Common AEs included nasopharyngitis, headache, upper respiratory tract infections, asthma, sinusitis, bronchitis, and fatigue. The incidence of asthma exacerbations and worsening was higher in the placebo groups compared with the mepolizumab groups.

3.7.2 Serious Adverse Events

In both trials, the proportion of patients reporting an SAE was higher in the placebo groups compared with the mepolizumab groups (MENSA, 14% versus 8%; SIRIUS, 18% versus 1%). The most common SAE was asthma exacerbation or worsening.

3.7.3 Withdrawal Due to Adverse Events

There were few withdrawals due to adverse events (WDAEs) across both studies. In MENSA, one patient (< 1%) in the mepolizumab group and four patients (2%) in the placebo group withdrew due to an AE. In SIRIUS, three patients in each group withdrew due to an AE. There was no clear pattern of reason for WDAEs in any group.

3.7.4 Notable Harms

Injection-site reactions occurred infrequently among treatment groups, but were more common in the mepolizumab group compared with the placebo group (MENSA, 9% versus 4%; SIRIUS, 6% versus 3%). All injection-site reactions were reported as mild or moderate in intensity. Systemic allergic reactions occurred infrequently and were experienced by similar proportions of patients in the mepolizumab and placebo groups in both trials (MENSA, 2% for both groups; SIRIUS, 6% versus 5%). Serious infections were reported in 3% of patients in both treatment groups in MENSA, and in 1% of patients in the mepolizumab group and 6% of patients in the placebo group in SIRIUS. Opportunistic infection was reported in 2% of patients in the mepolizumab group in MENSA, and 2% of patients in the placebo group in SIRIUS. Cardiac disorders were reported for similar proportions of patients in the mepolizumab and placebo groups (MENSA, 2% versus 3%; SIRIUS, 3% versus 5%). Malignant neoplasms were reported in three patients (5%) in the placebo group in SIRIUS and in no patients in the remaining groups.

TABLE 20: HARMS

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
AEs				
Patients With > 0 AEs, n (%)	152 (78)	158 (83)	57 (83)	61 (92)
Common AEs (≥ 10% Patients), n (%)				
Nasopharyngitis	33 (17)	46 (24)	10 (14)	10 (15)
Headache	39 (20)	33 (17)	14 (20)	14 (21)
URTI	24 (12)	27 (14)	3 (4)	5 (8)
Asthma	13 (7)	29 (15)	2 (3)	8 (12)
Sinusitis	18 (9)	18 (9)	7 (10)	6 (9)
Bronchitis	9 (5)	18 (9)	7 (10)	6 (9)
Fatigue	5 (3)	9 (5)	7 (10)	4 (6)
SAEs				
Patients With > 0 SAEs, n (%)	16 (8)	27 (14)	1 (1)	12 (18)
Common SAEs, n (%)				
Asthma	5 (3)	14 (7)	0	7 (11)
WDAEs				
WDAEs, n (%)	1 (< 1)	4 (2)	3 (4)	3 (5)
Notable Harms, n (%)				
Injection-site reaction	17 (9)	7 (4)	4 (6)	2 (3)
Systemic allergic reaction	3 (2)	4 (2)	4 (6)	3 (5)
Serious infection	6 (3)	5 (3)	1 (1)	4 (6)

	MENSA (MEA115588)		SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Opportunistic infection	3 (2)	0	0	1 (2)
Cardiac disorder	4 (2)	5 (3)	2 (3)	3 (5)
Malignancy	0	0	0	3 (5)

AE = adverse event; SAE = serious adverse event; SC = subcutaneous; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

4. DISCUSSION

4.1 Summary of Available Evidence

Two international, manufacturer-sponsored, phase 3, double-blind, placebo-controlled randomized trials met the inclusion criteria for this systematic review. MENSA (N = 576) was a 32-week study that evaluated the efficacy and safety of mepolizumab 100 mg SC and mepolizumab 75 mg IV once every four weeks as adjunctive therapy in patients with SEA. SIRIUS (N = 135) was a 24-week corticosteroid-sparing study that evaluated the effect of mepolizumab 100 mg SC once every four weeks in reducing OCS use in patients with SEA. Both studies enrolled patients at least 12 years of age with documented asthma meeting specific peripheral blood eosinophil counts (≥ 150 cells/mcL at visit 1 or ≥ 300 cells/mcL in the past 12 months) who were on regular treatment with high-dose ICS and an additional controller medication (e.g., LABA, leukotriene receptor antagonist, theophylline). In SIRIUS, eligible patients were to be using OCS at a dose between 5 mg/day and 35 mg/day. The primary end point in MENSA was the rate of clinically significant exacerbations (requiring systemic corticosteroids, hospitalization, or emergency department visits) at week 32. The primary end point in SIRIUS was the percentage reduction of OCS dose during weeks 20 to 24 compared with baseline dose while maintaining asthma control. Patients who completed the MENSA and SIRIUS trials had the option of participating in a 12-month open-label safety study (MEA115661, N = 651), where all patients received mepolizumab 100 mg SC once every four weeks (APPENDIX 6).

A phase 2/3 study (DREAM, N = 616) evaluated the efficacy and safety of various IV doses of mepolizumab and is summarized in APPENDIX 7. As the Health Canada–approved dose for mepolizumab is 100 mg SC once every four weeks, only trials that included this dosing regimen were included in this review.

Limitations of MENSA and SIRIUS included the relatively short duration of the studies to evaluate asthma exacerbations, the potential for improved compliance to background therapy in a clinical trial setting compared with real life as evidenced by improvements in the placebo groups, and the uncertainty regarding appropriate selection criteria to identify SEA patients.

4.2 Interpretation of Results

4.2.1 Efficacy

The inclusion criteria for SIRIUS and MENSA were similar, with the exception that SIRIUS had a requirement that patients be on regular treatment with OCS. A blood eosinophil cut-off of ≥ 150 cells/mcL at screening was selected based on a post hoc analysis of data from DREAM, which

demonstrated that peripheral blood eosinophil counts of ≥ 150 cells/mcL at screening in combination with clinical characteristics of asthma was a predictor of treatment response to IV mepolizumab, while sputum eosinophil counts of ≥ 3% at screening was not a good predictor.[28,29] An additional analysis of placebo patients from DREAM suggested that the majority (85%) of patients with peripheral eosinophil counts of ≥ 150 cells/mcL at screening remained above the 150 mark over the following year.[29] In MENSA, subgroup analyses of the primary end point (rate of clinically significant exacerbations) suggested that patients with higher screening blood eosinophil counts had a greater reduction in exacerbations with mepolizumab 100 mg SC than with placebo (≥ 150 cells/mcL versus < 150 cells/mcL), while there was no greater reduction demonstrated in patients with ≥ 300 cells/mcL in the past year compared with patients who did not. According to the clinical expert consulted for this review, peripheral eosinophil counts are not the best indicator of airway eosinophil levels, and a cut-off of 150 cells/mcL is relatively low to define an SEA population. However, patients enrolled in MENSA and SIRIUS were on regular treatment with high-dose ICS and OCS (100% of patients in SIRIUS, 30% of patients in MENSA), and were still exhibiting blood eosinophil counts of at least 150 cells/mcL along with other asthma disease characteristics, which makes the 150 cells/mcL cut-off less of a limitation.

According to the clinical expert involved in the review, baseline characteristics in both studies were typical of patients with severe asthma, and the FEV_1 reversibility was significant (> 400 mL). However, the age of patients was higher than what would be expected (mean about 50 years) in a disease that affects the younger population. Few adolescent patients (12 years to 17 years) were enrolled in both studies (4% in MENSA, 2% in SIRIUS), and therefore, the Health Canada indication for mepolizumab 100 mg SC is restricted to adult patients. A phase 2 study is currently in progress to characterize the pharmacokinetic properties of mepolizumab 40 mg SC and 100 mg SC in children 6 to 11 years.[30] In both MENSA and SIRIUS, there were differences between mepolizumab and placebo groups in the number of exacerbations in the past year and in screening pre-bronchodilator and post-bronchodilator FEV_1. MENSA adjusted for exacerbations in their statistical modelling, but SIRIUS did not.

The rate of clinically significant asthma exacerbations was evaluated as a primary end point in MENSA, a 32-week study. The clinical expert noted that a 52-week study would have been better to assess asthma exacerbations, as exacerbations fluctuate with changing seasons. In MENSA, there was a statistically significant reduction (53%) in the rate of clinically significant exacerbations with mepolizumab 100 mg SC compared with placebo in patients on background therapy with a high-dose ICS and an additional controller medication. Exacerbations requiring hospitalization or emergency department visit were reduced by 61%, while exacerbations requiring hospitalization were reduced by 69%. However, there is uncertainty regarding the true benefit of mepolizumab in reducing the annual rate of exacerbations due to the shorter length of trials.

Patients with severe asthma may require regular treatment with OCS, and long-term use of OCS may be accompanied by adverse side effects including weight gain, hypertension, osteoporosis, diabetes, and cardiovascular disease.[31] There is concern among patients regarding the use of OCS due to these physical changes and their impact on psychological and emotional well-being (APPENDIX 1). Therefore, an important goal of treating severe asthma patients on regular OCS treatment is to reduce the OCS dose to minimize unwanted side effects. SIRIUS was a corticosteroid reduction study where patients who were taking OCS at 5 mg/day to 35 mg/day underwent incremental dose reductions until asthma symptoms (based on PEF, nighttime awakenings, rescue medication use, and ACQ-5 score) precluded an additional reduction. In SIRIUS, there were statistically significant greater odds of achieving a reduction from baseline in OCS dose with mepolizumab than with placebo (OR 2.39; 95% CI, 1.25 to 4.56; P = 0.008). Patients in the placebo group (11%) were also able to achieve a 90% to 100% reduction in OCS

dose, although the proportion was less than in the mepolizumab group (23%). This difference may be due to better adherence to background therapy during the trial or seasonal fluctuations in asthma exacerbation severity. Secondary end points in SIRIUS supported the primary end point in that patients in the mepolizumab group had a statistically significantly greater chance of achieving a ≥ 50% reduction in daily OCS dose and achieving a reduction in daily OCS dose to ≤ 5 mg/day. According to the clinical expert, these are meaningful reductions in OCS dose.

Pulmonary function as measured by FEV_1 and PEF are widely used to assess the efficacy of drug treatments for asthma in clinical trials, and pre-bronchodilator FEV_1 has been considered to be the most suitable variable when measuring asthma control.[32] In MENSA, the mean change from baseline pre-bronchodilator FEV_1 at week 32 was statistically significantly greater in the mepolizumab group than in the placebo group (mean difference 98 mL; 95% CI, 11 to 184; *P* = 0.028), though this end point fell below a non-significant parameter in the hierarchy. A mean improvement from baseline in pre-bronchodilator FEV_1 of 70 mL was seen in the placebo group compared with an improvement of 204 mL in the mepolizumab group. The improvement in pre-bronchodilator FEV_1 observed in the placebo group could potentially be due to improved adherence to background therapies during the clinical trial. In SIRIUS, there was no certain difference in improvement from baseline at week 24 between mepolizumab and placebo groups in pre-bronchodilator FEV_1 (mean difference 114 mL; 95% CI, –42 to 271). There is no certain MCID for FEV_1, although values ranging from 100 mL to 230 mL have been reported (APPENDIX 5). Change from baseline in morning PEF at end of study was reported descriptively as four-week aggregated data in both studies; although results from MENSA suggested a greater improvement in the mepolizumab group than in the placebo group, results from SIRIUS were less certain (MENSA, mean difference 138 L/min; 95% CI, 43 to 232; SIRIUS, mean difference 128 L/min; 95% CI, –8 to 264). Some trialists have used a value of 25 L/min as an MCID for PEF values among patients with asthma; however, no research seems to support the use of this cut-off point (APPENDIX 5).

Health-related quality of life was another key efficacy outcome, and severe asthma patients cited that their day-to-day lives were impacted by the disease (APPENDIX 1). In MENSA and SIRIUS, quality of life was measured using the SGRQ, which was developed to assess impaired health and perceived well-being in patients with chronic airflow limitation. Though this is not an asthma-specific questionnaire, it has been validated in asthma patients, and the MCID has been reported to be an improvement of four points (APPENDIX 5). In both studies, there was a greater improvement from baseline in SGRQ at the end of the treatment period in the mepolizumab group compared with the placebo group, and a greater proportion of patients achieved a minimum four-point improvement in the mepolizumab groups compared with the placebo groups. In MENSA, placebo patients also demonstrated a clinically significant improvement from baseline in SGRQ score (mean change –9.2), and this may be due to placebo effects or improved adherence to background therapy, as mentioned earlier. The clinical expert noted that since the SGRQ is not an asthma-specific questionnaire, it is not used as often in clinical practice as asthma-specific questionnaires such as the Asthma Quality of Life Questionnaire.

While current therapies do provide some relief from symptoms, patients expressed a desire for improved control of asthma symptoms with new therapies (APPENDIX 1). In MENSA and SIRIUS, the ACQ-5 was used to assess symptom control, which is a shortened version of the full ACQ containing only five items on asthma symptoms (nighttime awakenings, symptom severity upon awakening, activity limitation due to asthma, shortness of breath due to asthma, and wheezing within the past week). In both MENSA and SIRIUS, patients had a great improvement from baseline in ACQ-5 score at the end of the treatment period in the mepolizumab group compared with the placebo group (mean difference –

0.44 to –0.52). The estimated MCID for all versions of the ACQ has been reported to be approximately 0.5 (APPENDIX 5).

Patients expressed how asthma symptoms have affected them negatively through increased emergency room visits in the past year and reduced performance at work or school (APPENDIX 1). In MENSA and SIRIUS, the proportion of exacerbations requiring emergency room visits or doctor visits was similar between the mepolizumab and placebo groups, but due to the higher number of exacerbations in the placebo groups compared with the mepolizumab groups (MENSA, 216 versus 116; SIRIUS, 68 versus 47), unscheduled resource use was higher in the placebo group. With regard to days taken off school and work due to asthma symptoms, numbers were generally low and balanced between mepolizumab and placebo groups in both studies, with the exception of days off work in SIRIUS, where placebo patients had a higher mean days off work than the mepolizumab group (5.7 versus 2.5).

Omalizumab is an anti-immunoglobulin E antibody that has a Health Canada indication for the treatment of adults and adolescents with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen whose symptoms are inadequately controlled with ICS.[12] The proportion of patients who had previously used omalizumab was low in MENSA and higher in SIRIUS (13% in MENSA; 33% in SIRIUS), and the majority of these patients had stopped treatment with omalizumab due to lack of efficacy. In MENSA, subgroup analysis of the primary end point based on previous use of omalizumab did not reveal differences in the reduction of exacerbations with mepolizumab compared to placebo. The clinical expert noted that this is not unexpected, as omalizumab and mepolizumab exert their effects through different mechanisms of action. When the primary end point was analyzed by baseline immunoglobulin E concentration, there was no reduction in clinically significant exacerbations with mepolizumab versus placebo for patients with a baseline immunoglobulin E ≤ 30 U/mL, while patients with baseline immunoglobulin E levels of > 30 U/mL showed similar reductions with mepolizumab versus placebo. The clinical expert noted that this may be due to the fact that allergic asthma (as evidenced by higher immunoglobulin E levels) would also have an eosinophilic component.

There were no direct head-to-head trials of mepolizumab and other therapies for severe asthma identified in this review. Mepolizumab is the only drug approved in Canada for the treatment of SEA; however, as severe allergic asthma may also have an eosinophilic component, there is an overlapping patient population of severe asthmatics who would be eligible for both mepolizumab and omalizumab. Based on a manufacturer-sponsored study (IDEAL, N = 791), approximately 26.5% of patients eligible for omalizumab would also be eligible for mepolizumab, while approximately 50% of patients eligible for mepolizumab would also be eligible for omalizumab. The manufacturer submitted an indirect treatment comparison (ITC) to evaluate the relative efficacy of mepolizumab and omalizumab in patients with severe asthma who would be eligible for both therapies (APPENDIX 8). The results of the ITC suggested that [redacted]. However, there were serious limitations with the analyses due to the limited number of studies included in the analyses and a high degree of uncertainty associated with the findings.

4.2.2 Harms

The overall incidence of AEs was slightly higher in the placebo group than in the mepolizumab group in MENSA and SIRIUS because of an increased incidence of asthma AEs with placebo. The most common AEs were nasopharyngitis and headache. The incidence of SAEs was higher in the placebo group

compared with the mepolizumab group in both studies, again due to the occurrence of severe asthma AEs. WDAEs were low and balanced between treatment groups.

Notable harms including injection-site reactions, systemic allergic reactions, serious infections, opportunistic infections, cardiac disorders, and malignancies were low and balanced across treatment groups in both studies. Due to the short-term nature of both studies (32 weeks for MENSA, 24 weeks for SIRIUS), it would be difficult to assess malignancies and cardiac disorders.

Patients who completed MENSA and SIRIUS had the option of enrolling in a 52-week open-label extension study (MEA115666, N = [redacted]) where they received mepolizumab 100 mg SC once every four weeks (APPENDIX 6). The AE profile from the long-term extension was similar to what was observed in MENSA and SIRIUS.

Patients who completed the 52-week DREAM study had the option of enrolling in an ongoing long-term extension study after at least 10 months after their last dose of IV mepolizumab (MEA115666, N = [redacted]), where they received mepolizumab 100 mg SC once every four weeks (APPENDIX 7). At the time of the interim report, the mean (SD) time since completion of DREAM was 18.1 (2.7) months. The AE profile during this long-term extension study was also similar to what was observed in MENSA, SIRIUS, and MEA115666.

4.3 Potential Place in Therapy[1]

Asthma is a reversible airway disease characterized by eosinophilic inflammation. The mainstay of treatment for asthma is ICS. Approximately 5% to 10% of patients with asthma are deemed to have severe or refractory asthma, meaning they require high-dose ICS (and often add-on therapies such as LABAs, leukotriene receptor antagonists, or long-acting muscarinic antagonists) and oral prednisone.[33] Patients with poorly controlled asthma are very limited in their day-to-day lives, including missing work more often and using more health care resources.[33] The long-term adverse effect profile of prednisone (such as osteoporosis, hypertension, diabetes, adrenal suppression) and the associated cost to the health care system are well known to physicians and are reasons to want to minimize its usage.

One alternative to prednisone was available to severe or refractory patients, omalizumab (Xolair), but this treatment was reserved for patients with persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled on ICS (i.e., severe persistent allergic asthma) and thus is not what all severe or refractory corticosteroid depend patients need.

Based on the clinical trials included in this review, mepolizumab has shown promising results for patients with severe or refractory asthma, in particular for those patients who require ongoing use of oral prednisone. It represents an alternative to prednisone and its extensive adverse effects and has the potential for better asthma control in a patient population that has been without treatment options for many years.

Suitable patients to receive mepolizumab could be identified in practice based on spirometry, demonstrating reversibility or fluctuation on and off prednisone. Spirometry is accessible, and hand-held

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

devices could be used in offices to follow flow rates. Peripheral eosinophil levels would also be routinely checked.

There is currently insufficient evidence for or experience with mepolizumab to say whether the drug can be discontinued after a certain period of treatment. However, if the treatment leads to a decrease or stopping of prednisone, the benefit for patients may be greater by staying on mepolizumab than by risking the known and extensive side effects of prednisone and the cost of poorly controlled asthma.

5. CONCLUSIONS

Two international, manufacturer-sponsored, phase 3, double-blind, placebo-controlled, randomized controlled trials met the inclusion criteria for this systematic review. MENSA (N = 576) was a 32-week study that evaluated the efficacy and safety of mepolizumab 100 mg SC and mepolizumab 75 mg IV once every four weeks as adjunctive therapy in patients with SEA. SIRIUS (N = 135) was a 24-week corticosteroid-sparing study that evaluated the effect of mepolizumab 100 mg SC once every four weeks in reducing OCS use in patients with SEA. Results from MENSA suggested that mepolizumab 100 mg SC is associated with a statistically significant reduction in the rate of clinically significant asthma exacerbations compared with placebo in patients currently on high-dose ICS and an additional asthma controller meeting screening eosinophil criteria of ≥ 150 cells/mcL at screening or ≥ 300 cells/mcL in the past year. Results from SIRIUS suggested that mepolizumab 100 mg SC is associated with a greater likelihood of a reduction in daily OCS dose compared with placebo in patients with SEA who were taking OCS at a dose of 5 mg/day to 35 mg/day. Due to the increased number of exacerbations in the placebo groups compared with the mepolizumab groups, there was greater unplanned health resource use and OCS use in the placebo groups. AE data were generally similar between groups, except for a higher proportion of patients in the placebo groups experiencing asthma-related AEs than in the mepolizumab groups. Safety results from Study MEA115666, a 52-week open-label extension study of patients completing MENSA and SIRIUS, were similar to the AE profile observed in the individual studies.

There were no direct head-to-head trials of mepolizumab and other therapies for severe asthma identified in this review. The manufacturer submitted an ITC to evaluate the relative efficacy of mepolizumab and omalizumab in patients with severe asthma who would be eligible for both therapies. [redacted]. However, there were serious limitations with the analyses due to the limited number of studies included and a high degree of uncertainty associated with the findings.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input
Two patient groups submitted input: Ontario Lung Association, and Asthma Society of Canada/National Asthma Patient Alliance.

The Ontario Lung Association is a charitable organization that assists and empowers persons living with or caring for others with lung disease, including asthma. The Ontario Lung Association works alongside nine other provincial lung associations and the Canadian Lung Association. This organization receives sponsorship for educational and research purposes from 10 pharmaceutical companies, including GlaxoSmithKline, as well as the Ontario Home Respiratory Services Association.

The Asthma Society of Canada is a national, charitable, volunteer-supported organization whose aim is to enhance the quality of life and health of persons living with asthma and associated allergies. The Society provides health education services and advocates on behalf of Canadians with asthma through its grassroots patient group (National Asthma Patient Alliance) and engages in research to improve asthma prevention and management strategies. This organization receives financial support through educational grants from GlaxoSmithKline and an additional 12 pharmaceutical manufacturers.

Both the Ontario Lung Association and the Asthma Society of Canada have declared no conflict of interest in the preparation of their submissions. The Asthma Society of Canada disclosed that it had previously requested and received a medical briefing regarding Nucala from GlaxoSmithKline. It was also disclosed that the author of the patient input submission for Society is employed at SCRIPT, a medical communications company. GlaxoSmithKline is not listed as one of SCRIPT's clients on its website.

2. Condition-Related Information
Patient impact information provided by the Ontario Lung Association was based on five online surveys completed by persons living with asthma and input from a certified respiratory educator. Details relating to the number of survey respondents, their demographics, or their asthma severity levels were not provided. Conversely, information provided by the Asthma Society of Canada was drawn from a mixed-methods study involving 24 in-depth personal interviews and an online quantitative survey of 200 individuals with severe asthma conducted by this organization in 2014 (*Severe Asthma: The Canadian Patient Journey*). Study participants consisted of individuals aged 18 years and older who live with controlled or uncontrolled severe asthma and reside in one of four urban centres across three Canadian provinces (Alberta, Ontario, and Quebec); the number of surveyed participants with uncontrolled severe asthma (as compared with controlled severe asthma) was not specified.

While members of both patient groups identified a number of common symptoms and challenges experienced by persons living with asthma, including shortness of breath, coughing, wheezing, difficulty fighting infections, and fatigue, the Asthma Society of Canada placed particular emphasis on the impact of severe asthma on patients' daily lives. Namely, severe asthma affected patients' day-to-day lives in the following aspects: 71.4% of survey respondents reported decreased physical activity, 55.1% reported reduced performance at work or school, 64.6% of respondents experienced restricted social interaction due to stigma, and 48.0% of respondents reported increased emergency room visits in the 12 months preceding

this study, with one in five individuals requiring hospitalization. Activity restriction as a result of uncontrolled asthma symptoms was of particular concern, with one study participant stating:

> *"I can't even take my son hiking because of my health. My limitations affect other people and it makes me angry that I can't do the things others can and that I used to be able to do."*

The burden of this condition may extend beyond the patient and impact persons who must care for or live with an adult with severe asthma; however, the impact on caregivers was not specifically assessed by the Asthma Society of Canada or Ontario Lung Association. Based on participant comments relating to their interactions with others, the Asthma Society suggested that caregivers may experience an emotional burden (e.g., stress, anxiety) or financial impact (e.g., time off work) as a result of having to care for a person with severe asthma. Interruptions to sleep and other aspects of a caregiver's daily life may also be adversely affected.

3. Current Therapy–Related Information

Current treatment options for the management of asthma symptoms include a combination of long-term controller medications (e.g., inhaled corticosteroids [ICS], leukotriene receptor antagonists, long-acting bronchodilators, and oral corticosteroids [OCS]) or fast-acting reliever medications for acute symptoms (e.g., short-acting bronchodilators). Ontario Lung Association survey respondents noted that while current therapies do provide some relief from symptoms, including shortness of breath, cough, poor appetite, and the decreased ability to fight infections, they also reported decreased energy levels associated with medication use and expressed discontent relating to losses in productivity as a result of medical appointments and associated travel time. In addition, respondents wished for a greater improvement of asthma symptoms with therapy and a reduction in overall medication burden.

According to the study conducted by the Asthma Society, severe asthma patients did not appear to use their medications as directed and were not always well prepared to manage their symptoms; cited barriers to optimal asthma control included a lack of efficacy, unpleasant side effects, patients' misperception that their asthma was well controlled, and financial constraints in access to medication. The Asthma Society expressed particular concern regarding the use of OCS in patients who do not achieve adequate asthma control with an ICS drug. Namely, it reports that systemic corticosteroids are associated with short-term and long-term adverse effects, both in terms of physical changes and in terms of patients' psychological and emotional well-being. Given that severe asthma patients are unable to adequately control their symptoms and exacerbations with the use of currently available therapies, the Asthma Society highlights that severe asthma by definition carries with it an unmet need for therapy options that go beyond the standard of care.

4. Expectations About the Drug Being Reviewed

There were no patients from the Ontario Lung Association or Asthma Society patient group studies that reported previous use or experience with Nucala; however, both groups had a number of unmet needs that, if addressed, could make a positive impact on severe asthma patients' lives.

Based on no experience with the drug under review, the Ontario Lung Association indicated that asthma patients would experience an improved quality of life and improved lung function if a new drug led to reduced shortness of breath, reduced coughing, reduced fatigue, improved appetite, an improved ability to fight infections, and higher energy levels. In the Asthma Society's survey, severe asthma patients indicated that in order to achieve optimal asthma control, they wished to gain normal functioning in completing everyday tasks (e.g., household activities, walking), reduced emergency department visits and hospitalization, decreased sleep disturbances, symptom-free exercise, and improved work performance.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	January 26, 2016
Alerts:	Weekly search updates until May 18 2016
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
Oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(nucala* or mepolizumab* or bosatria* or SB240563 or SB-240563 or 90Z2UFOE52).ti,ab,ot,rn,hw,nm,kf.
2	196078-29-2.rn,nm.
3	1 or 2
4	3 use pmez
5	(nucala* or mepolizumab* or bosatria* or SB240563 or SB-240563 or 90Z2UFOE52).ti,ab,kw.
6	*mepolizumab/
7	5 or 6
8	7 use oemezd
9	4 or 8
10	asthma*.ti.
11	(interleukin-5* or IL-5*).ti.
12	10 and 11
13	12 not 9
14	9 or 13
15	remove duplicates from 14
16	15 not conference abstract.pt.
17	exp animals/
18	exp animal experimentation/ or exp animal experiment/
19	exp models animal/
20	nonhuman/
21	exp vertebrate/ or exp vertebrates/
22	or/17-21
23	exp humans/
24	exp human experimentation/ or exp human experiment/
25	or/23-24
26	22 not 25
27	16 not 26

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in Medline. Same MeSH, keywords, limits, and study types used as per Medline search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per Medline search.

Grey Literature

Dates for Search:	January 2016
Keywords:	Nucala, mepolizumab
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Kanagalingam et al. 2015[34]	Commentary
Robinson et al. 2013[35]	
Haldar et al. 2009[36]	Intervention
Nair et al. 2009[37]	
Pavord et al. 2012[28]	
Clinical Study Report: MEA115666[38]	Long-term extension
Clinical Study Report: MEA115661[39]	
Flood-Page et al. 2007[40]	Patient population

APPENDIX 4: DETAILED OUTCOME DATA

Subgroup Analyses

TABLE 21: SUBGROUP ANALYSES OF CLINICALLY SIGNIFICANT EXACERBATIONS IN MENSA

	MENSA (MEA115588)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)
Primary Analysis		
Exacerbation rate/year	0.83	1.74
Rate ratio (95% CI)	0.47 (0.35 to 0.64) *P* < 0.001	
Exacerbations in Past Year		
2 Exacerbations in Past Year		
n	74	90
Exacerbation rate/year	0.58	1.09
Rate ratio (95% CI)	0.53 (0.30 to 0.94)	
3 Exacerbations in Past Year		
n	48	46
Exacerbation rate/year	0.48	1.63
Rate ratio (95% CI)	0.30 (0.16 to 0.55)	
> 4 Exacerbations in Past Year		
n	72	55
Exacerbation rate/year	1.43	3.22
Rate ratio (95% CI)	0.44 (0.29 to 0.69)	
Baseline Maintenance OCS Therapy		
No		
n	142	147
Exacerbation rate/year	0.55	1.60
Rate ratio (95% CI)	0.34 (0.23 to 0.51)	
Yes		
n	52	44
Exacerbation rate/year	1.73	2.16
Rate ratio (95% CI)	0.80 (0.49 to 1.29)	
Blood Eosinophil Level at Screening, cells/mcL		
< 150		
n	35	21
Exacerbation rate/year	1.20	1.31
Rate ratio (95% CI)	0.91 (0.44 to 1.90)	
150 to < 300		
n	49	59
Exacerbation rate/year	0.62	1.28
Rate ratio (95% CI)	0.48 (0.27 to 0.86)	
300 to < 500		
n	45	48
Exacerbation rate/year	0.78	1.63

	MENSA (MEA115588)	
	Mepolizumab 100 mg SC (n = 194)	Placebo (n = 191)
Rate ratio (95% CI)	0.48 (0.26 to 0.89)	
≥ 500		
n	61	60
Exacerbation rate/year	0.47	2.26
Rate ratio (95% CI)	0.21 (0.12 to 0.36)	
Blood Eosinophil Inclusion Criteria		
≥ 300 cells/mcL in Past 12 Months — Yes		
n	146	121
Exacerbation rate/year	0.94	1.64
Rate ratio (95% CI)	0.57 (0.41 to 0.80)	
≥ 300 cells/mcL in Past 12 Months — No		
n	48	70
Exacerbation rate/year	0.50	1.89
Rate ratio (95% CI)	0.27 (0.14 to 0.52)	
≥ 150 cells/mcL at Screening — Yes		
n	155	167
Exacerbation rate/year	0.67	1.75
Rate ratio (95% CI)	0.38 (0.27 to 0.53)	
≥ 150 cells/mcL at Screening — No		
n	35	21
Exacerbation rate/year	1.20	1.31
Rate ratio (95% CI)	0.91 (0.44 to 1.90)	
≥ 300 cells/mcL in Past 12 Months Only		
n	39	23
Exacerbation rate/year	1.25	1.52
Rate ratio (95% CI)	0.82 (0.38 to 1.77)	
≥ 150 cells/mcL at Screening Only		
n	48	69
Exacerbation rate/year	0.51	1.92
Rate ratio (95% CI)	0.26 (0.14 to 0.52)	
Both ≥ 300 cells/mcL in Past 12 Months and ≥ 150 cells/mcL at Screening		
n	107	98
Exacerbation rate/year	0.74	1.62
Rate ratio (95% CI)	0.46 (0.31 to 0.67)	
Baseline IgE Concentration		
≤ 30 U/mL		
n	24	28
Exacerbation rate/year	0.31	0.31
Rate ratio (95% CI)	1.00 (0.47 to 2.10)	
> 30 U/mL to ≤700 U/mL		
n	130	129
Exacerbation rate/year	0.68	1.66
Rate ratio (95% CI)	0.41 (0.28 to 0.60)	

	MENSA (MEA115588)	
	Mepolizumab 100 mg SC (n = 194)	**Placebo (n = 191)**
> 700 U/mL		
n	28	25
Exacerbation rate/year	0.55	1.59
Rate ratio (95% CI)	0.35 (0.13 to 0.90)	
Previous Use of Omalizumab		
Yes		
n	25	21
Exacerbation rate/year	1.40	2.36
Rate ratio (95% CI)	0.59 (0.28 to 1.26)	
No		
n	169	170
Exacerbation rate/year	0.74	1.62
Rate ratio (95% CI)	0.46 (0.33 to 0.63)	

CI = confidence interval; IgE = immunoglobulin E; OCS = oral corticosteroid; SC = subcutaneous.
Source: MENSA Clinical Study Report.[1]

TABLE 22: SUBGROUP ANALYSES OF PERCENTAGE REDUCTION FROM BASELINE IN ORAL CORTICOSTEROID DOSE IN SIRIUS

	SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC (n = 69)	Placebo (n = 66)
Primary Analysis		
OR (95% CI)[a]	2.39 (1.25 to 4.56)	
Baseline OCS Dose		
5 mg to < 10 mg		
N	22	17
OR (95% CI)[a]	3.56 (0.97 to 13.11)	
10 mg to < 15 mg		
N	28	22
OR (95% CI)[a]	1.07 (0.37 to 3.05)	
≥ 15 mg		
N	19	27
OR (95% CI)[a]	6.25 (1.67 to 23.38)	
Blood Eosinophil Level at Screening, cells/mcL		
< 150		
N	15	18
OR (95% CI)[a]	6.87 (1.53 to 30.88)	
150 to < 300		
N	18	20
OR (95% CI)[a]	2.03 (0.53 to 7.75)	
300 to < 500		
N	16	9
OR (95% CI)[a]	3.64 (0.69 to 19.24)	
≥ 500		
N	20	19
OR (95% CI)[a]	1.01 (0.31 to 3.31)	
Blood Eosinophil Inclusion Criteria		
≥ 300 cells/mcL in Past 12 Months — Yes		
N	50	42
OR (95% CI)[a]	4.35 (1.86 to 10.17)	
≥ 300 cells/mcL in Past 12 Months — No		
N	19	24
OR (95% CI)[a]	1.16 (0.37 to 3.64)	
≥ 150 cells/mcL at Screening — Yes		
N	61	60
OR (95% CI)[a]	1.92 (0.97 to 3.81)	
≥ 150 cells/mcL at Screening — No		
n	8	6
OR (95% CI)[a]	13.29 (0.97 to 188.50)	

CI = confidence interval; OCS = oral corticosteroid; OR = odds ratio; SC = subcutaneous.
Source: SIRIUS Clinical Study Report.[2]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity and minimal clinically important difference (MCID) of the following outcome measures:

- forced expiratory volume in one second (FEV_1)
- peak expiratory flow (PEF)
- St. George's Respiratory Questionnaire (SGRQ)
- Asthma Control Questionnaire 5 (ACQ-5)
- EuroQol 5-Dimensions questionnaire (EQ-5D)
- SGRQ mapping to EQ-5D utilities.

Findings

The above outcome measures are briefly summarized in Table 23.

TABLE 23: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Evidence of Validity	MCID (or Similar Parameter)	References
FEV_1	FEV_1 is the volume of air that can be forcibly expired in 1 second after a full inspiration.	Yes	MPPI: 10.4% change from baseline	Santanello et al. 1999[41]
PEF	PEF is the maximum flow rate achieved during a maximal forceful exhalation, starting from full lung inflation.	Yes	MPPI: 18.8 L/min	Santanello et al. 1999[41]
SGRQ	SGRQ is a disease-specific measure of HRQoL that consists of 50 items with 76 responses. It was developed for patients with chronic airflow limitation, including asthma. The questionnaire is divided into three dimensions: symptoms, activity, and impacts of the disease. The total score ranges from 0 to 100, where 0 indicates no impairment and 100 indicates greatest impairment.	Yes	4 units	Jones et al. 1992[42] Bourbeau et al. 2004[43]
ACQ-5	ACQ-5 is a shortened version of the original 7-item ACQ measure. This patient-reported assessment of the adequacy of asthma treatment comprises items relating exclusively to patient symptoms (nighttime awakenings, symptom severity upon awakening, activity limitation due to asthma,	Yes	0.5	Juniper et al. 2001[44] Juniper et al. 2005[45] Wyrwich et al. 2011[25]

Instrument	Type	Evidence of Validity	MCID (or Similar Parameter)	References
	shortness of breath due to asthma, and wheezing within the past week); items relating to rescue bronchodilator use and FEV_1 per cent of predicted normal, which are part of the original ACQ, are excluded from the ACQ-5. All items are scored on a 7-point scale, which ranges from 0 (indicating good control) to 6 (poor control). The overall score is the mean of all questions, with a high score indicating poor control.			
EQ-5D	EQ-5D is a general, non-disease-specific health-related quality of life questionnaire.	Yes	*Asthma:* unknown *General use:* 0.033 to 0.074 for index score	

ACQ-5 = Asthma Control Questionnaire (5-item version); EQ-5D = EuroQoL; FEV_1 = forced expiratory volume in 1 second; HRQoL = health-related quality of life; MCID = minimal clinically important difference; MPPI = minimal patient perceivable improvement; PEF = peak expiratory flow; SGRQ = St. George's Respiratory Questionnaire.

Forced Expiratory Volume in One Second

FEV_1 is the maximal amount of air forcefully exhaled in one second. The measured volume can be converted to a percentage of predicted normal value, which is adjusted based on height, weight, and race. The percentage of predicted FEV_1 is one of the most commonly reported pulmonary function tests.[20] Considered an acceptable primary end point (although recommended as a secondary clinical end point) by Health Canada,[46] FEV_1 is widely used in clinical trials to evaluate the effectiveness of asthma treatments.

Clinically, the percentage of predicted FEV_1 appears to be a valid marker for the degree of airway obstruction with asthma and other respiratory conditions, including chronic obstructive pulmonary disease and cystic fibrosis. Together with asthma symptoms and the use of inhaled short-acting $beta_2$ agonist, FEV_1 is used to classify the severity of asthma.[47,48] However, the extent to which FEV_1 values are associated with quality of life is uncertain, as researchers have reported variable correlations among adults and children with asthma, ranging from no association to strong associations.[49-52] Conversely, FEV_1 values appear to correlate well with certain final clinical outcomes, such as the likelihood of hospitalization.[53] Furthermore, FEV_1 values demonstrate high within-session repeatability: In a study of 18,526 adult patients, of whom 11% gave a history of physician-diagnosed asthma, 90% were able to reproduce FEV_1 within 120 mL.[54]

There appears to be limited published evidence relating to an MCID for the FEV_1 measure among adult patients with asthma. In one study of 281 adult asthmatic patients (baseline mean FEV_1, 2.30 ± 0.66 L/s), the authors calculated the minimal patient perceivable improvement (MPPI) for FEV_1 by comparing the average baseline FEV_1 scores with patient global ratings of change in asthma. Across all patients, the MPPI for FEV_1 was 230 mL, or 10.38% change from baseline. Males and females showed similar MPPI values, but older patients had a lower MPPI (170 mL) than younger individuals (280 mL) for FEV_1.[41]

Peak Expiratory Flow

PEF — sometimes referred to as peak expiratory flow rate, or PEFR — is defined as "the maximum flow achieved during an expiration delivered with maximal force starting from the level of maximal lung inflation."[21] It can be measured using a mechanical peak flow meter, in which case patients may be asked to record the PEF values in diaries. However, the published literature suggests that patient diaries are often unreliable among asthmatic patients, particularly children.[55-57] PEF may alternatively be measured using electronic peak flow meters, which automatically store and download measurements as needed. PEF is usually expressed in units of litres per minute (L/min) and sometimes as a percentage of the predicted normal value or as a change from baseline average values.[58]

PEF values appear to discriminate between patients with reversible and irreversible airflow obstruction.[59] PEF values also appear to be a valid clinical marker of airway responsiveness and asthma severity.[58] In addition, they seem to correlate well with other measures of lung function, including FEV_1,[60] although evidence that directly links PEF with quality of life is lacking.

Some trialists have used a value of 25 L/min as an MCID for PEF values among patients with asthma;[22,23] however, no research seems to support the use of this cut-off point. In one study of 281 adult asthmatic patients, researchers calculated the MPPI for PEF by comparing the average baseline PEF scores with patient global ratings of change in asthma. Across all patients, the MPPI for PEF was 18.8 L/min, with no differences in MPPI values by gender or age.[41] In another study, researchers noted a predicted PEF of about 12% to be a minimal clinically significant improvement among patients presenting to the emergency department with acute asthma exacerbation.[61]

St. George's Respiratory Questionnaire

SGRQ is a disease-specific measure of health-related quality of life that was specifically developed for patients with airway obstruction.[42] It was developed in 1992 to measure impaired health and perceived well-being in patients with airway disease and to meet the need for a sensitive measure of health-related quality of life.[43] The instrument has been used worldwide in studies and in clinical settings, and it appears to be a valid and reliable measure of health status among patients with chronic airflow limitation, including asthma and chronic obstructive pulmonary disease.[42,43] SGRQ includes questions regarding sleep disturbances, public embarrassment, and panic (which can be signs of depression or anxiety) as well as feeling like a nuisance to friends and family, employment, and recreation activities (which are indicative of social impact).[62]

The questionnaire contains 50 items and 76 weighted responses that are divided into three subscales: symptoms (8 items measuring the frequency of respiratory symptoms over a preceding period that may range one month to one year), activity (16 items measuring the disturbances to patients' daily physical activity), and impacts (26 items measuring the psychosocial impact of the disease).[63-65] Items are weighted using empirically derived weights in order to determine the SGRQ total score, which ranges from 0 to 100, where 0 indicates no impairment and 100 indicates worst possible health.[63,66] In addition to the total score, component scores for the symptoms, activity, and impacts domains can be calculated (also ranging from 0 to 100). Namely, for the symptoms domain, patients are asked to rate the appearance, frequency, and severity of respiratory symptoms (wheeze, breathlessness, cough, etc.) on a 5-point scale, where the low scores indicate no symptoms and high scores indicate more severe symptoms.[63] A number of items in the symptoms component relate to the frequency of symptoms over the previous year.[67] Responses on the other two domains are mostly yes/no in nature. The activity domain deals with mobility and physical activity problems that either cause or are limited by breathlessness.[63] Conversely, the impacts domain covers aspects relating to social functioning and

psychosocial disturbances resulting from the obstructive airway disease (employment, panic, medication, and side effects).[67] These social impacts may be particularly troubling aspects of disease among asthmatic patients.

Among patients with asthma, the generally accepted MCID for a change in total SGRQ from baseline is 4.0 units, and a decrease in score indicates an improvement in health-related quality of life.[68] However, this threshold for clinical significance of the SGRQ measure was derived based on patient judgment using data from a one-year study of nedocromil in moderate asthma;[69] namely, the difference in patients' SGRQ score from baseline to the end of the study was compared with their retrospective estimate of the treatment's efficacy (made at the end of the study), and a rank order correlation between patients' change in health status and judgment of treatment efficacy was then computed. Evidence of clinician judgment or criterion referencing to establish an MCID for the SGRQ measure among patients with asthma is currently lacking.[68]

Asthma Control Questionnaire 5

ACQ is a patient-reported instrument that measures the adequacy of asthma treatment; it consists of seven items, including five items on symptoms (nighttime awakenings, symptom severity upon awakening, activity limitation due to asthma, shortness of breath due to asthma, and wheezing within the past week), one item on rescue bronchodilator use, and one item on FEV_1 per cent of predicted normal.[24] The seven ACQ items were selected by 100 asthma experts from 18 countries, and all seven questions are scored on a 7-point scale, which ranges from 0 (indicating good control) to 6 (poor control). The overall score is the mean of all seven questions, with higher scores indicating poorer control.[24] Patients recall their relevant experiences during the previous seven days.

There are three shortened versions of the original seven-item ACQ. These include a five-item measure which includes only the symptoms items (ACQ-5), as well as two six-item variants (ACQ-6a, symptoms plus rescue bronchodilator use; and ACQ-6b, symptoms plus FEV_1 per cent of predicted normal).[25]

The original seven-item ACQ was initially validated in a nine-week observational study of 50 adults with symptomatic asthma.[24] In this study, researchers noted that the ACQ correlated well with the Asthma Quality of Life Questionnaire (Pearson correlation coefficient = 0.76). Further, the test–retest reliability of the instrument was high in patients whose asthma was stable between clinic visits (intra-class correlation coefficient = 0.90). The questionnaire was also responsive to change in unstable patients ($P < 0.0001$). The ACQ has also been validated in children with asthma,[70] and discriminates between patients with well-controlled asthma versus inadequately controlled asthma using an optimal cut-point score of 1.50 (positive predictive value = 0.88).[71]

Validation and agreement across the ACQ's shortened versions has also been investigated.[25,44,45] Namely, results from one validation study using data from the aforementioned nine-week observational study revealed that the omission of items relating to rescue bronchodilator use and FEV_1 per cent of predicted normal from the original measure did not alter the measurement properties or validity of the instrument; correlations were high between the ACQ and the abbreviated versions.[44] These findings were corroborated by two subsequent validation studies which were based on samples from a 26-week randomized controlled trial (n = 552) and a post hoc analysis of two large phase 3, randomized, multi-centre, placebo-controlled trials (n = 737 and n = 772).[25,45] Particularly, in the secondary analysis of the 26-week randomized controlled trial of 552 adults with asthma, the authors calculated an MCID value for the ACQ measure, as well as the three shortened versions, by regressing the change scores on

the ACQ on the Mini–Asthma Quality of Life Questionnaire using a geometric mean regression model.[45] The estimated MCID for all versions of the ACQ was approximately 0.5.

EuroQol 5-Dimensions Questionnaire

EQ-5D is a generic, non-disease-specific measure of health status.[72] The tool is based on self-report of five domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. There are three levels per domain in the original version: no problems, some or moderate problems, and extreme problems. Each combination of the five domains and three levels creates a unique health state description (243 in total). The index score is calculated by applying a country-specific, utility-function-based scoring algorithm to the EQ-5D health states. This algorithm attaches weights reflecting jurisdiction-specific preferences for each health state.[73] An index score of 1 represents best possible health and 0 represents dead, with the possibility of health states being valued as worse than dead (< 0). The EQ-5D is also accompanied by a visual analogue scale to provide a self-rating of overall health, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).[72]

Findings of a review on the psychometric properties of the EQ-5D measure revealed that evidence from seven studies generally supported the construct validity, test–retest reliability, and responsiveness of EQ-5D in asthma; there was also some evidence of ceiling effects among healthier asthma patients for this measure.[74] Moreover, the discriminant validity of the EQ-5D in terms of its ability to distinguish different levels of asthma control was examined in a cross-sectional sample of 157 asthmatic adults.[75] The authors of this study concluded that while the EQ-5D was able to discriminate across asthma control measures (ACQ scores and amount of rescue medication use), it did not differentiate well between self-reported control and levels of asthma severity.

The EQ-5D has demonstrated discriminant validity and responsiveness in patients with asthma, but not to the same extent as disease-specific measures such as Asthma Quality of Life Questionnaire or SGRQ.[74,76] An MCID for EQ-5D index or visual analogue scale scores in patients with asthma is lacking from the published literature; however, the MCID for the EQ-5D index score in general use ranges from 0.033 to 0.074.[77]

SGRQ Mapping to EQ-5D Utilities

Utility-based health-related quality of life measures, such as the EQ-5D, are frequently required for assessing the cost-effectiveness of new pharmacologic treatments, yet EQ-5D data may not be routinely collected, particularly alongside clinical trials. In such cases, a mathematical algorithm, or mapping technique, to estimate utility scores from a condition-specific health-related quality-of-life instrument such as the SGRQ may be useful. Although utility values may be elicited using such mapping techniques, caution should be taken in ensuring that a predictive algorithm is appropriately developed and validated.

Starkie et al.[78] have proposed a method to predict EQ-5D utility values using the SGRQ in patients with chronic obstructive pulmonary disease. In this study, the authors used regression equations (ordinary least squares, generalized linear model, and two-part model) to map SGRQ to EQ-5D index scores using demographic variables and SGRQ total, domain, or item scores. SGRQ and EQ-5D data were previously collected in a large randomized controlled trial comparing the efficacy of salmeterol/fluticasone versus salmeterol, fluticasone, and placebo in patients with moderate to very severe chronic obstructive pulmonary disease over three years; data were split non-randomly into an algorithm development sample (all non-US patients, 66% of sample) and a validation sample (all US patients, 33% of sample). Algorithms developed using the development sample were used to predict EQ-5D index scores in the

validation sample, and predictive ability was measured using the root-mean-square error (RMSE). Findings of this mapping study revealed that the ordinary least squares regression model performed favourably compared with more complex statistical models. However, the authors cautioned that while utility values may be elicited using this approach, the algorithm may not accurately predict utility for the worst and best health states. Until a better predicting mapping technique is developed, it is recommended that direct collection of utility values within clinical trials, using an instrument such as the EQ-5D, be performed.

While the algorithm developed by Starkie et al. may be useful in estimating utility values for patients with chronic obstructive pulmonary disease, similar mapping techniques for patients with asthma are currently lacking from the published literature. Therefore, the validity of using this mapping algorithm to obtain EQ-5D utilities in patients with asthma is highly uncertain.

Conclusion

Overall, FEV_1, PEF, SGRQ, ACQ-5, and EQ-5D appear to be validated outcomes for use in clinical trials of therapies for patients with asthma. The SGRQ and ACQ-5 measures seem to have a well-documented MCID value; a review of the literature did not find a validated MCID for the other outcomes.

APPENDIX 6: SUMMARY OF LONG-TERM EXTENSION STUDY OF MENSA AND SIRIUS (MEA115661)

Aim

To summarize the 52-week open-label extension study of patients enrolled in MENSA and SIRIUS (MEA115661).[79]

Findings

MEA115661 (N = 651) was a 52-week, open-label extension study that enrolled patients who completed MENSA or SIRIUS in order to evaluate the long-term safety of mepolizumab 100 mg subcutaneous (SC). Patients were administered mepolizumab 100 mg SC once every four weeks. Safety outcomes were the primary focus of this study. Efficacy outcomes that were assessed included the annualized rate of exacerbations, ACQ-5 score, and FEV_1. The last visit (exit visit) in MENSA and SIRIUS was considered the baseline visit (visit 1) for this study. Patients who met the inclusion criteria received their first mepolizumab dose at visit 1. Patients were expected to continue background controller therapy for the duration of the study. The study period was from May 27, 2013, to March 13, 2015.

Patient Disposition

More than 90% of patients who were randomized and treated in MENSA and SIRIUS entered the open-label extension. A total of 651 patients were enrolled in MEA115661, and 18 patients (3%) withdrew from the study. The most common reasons for withdrawal were an adverse event (AE) (six patients) and lack of efficacy (four patients).

TABLE 24: PATIENTS ENROLLED IN MEA115661 FROM MENSA AND SIRIUS

	MENSA (MEA115588)			SIRIUS (MEA115575)	
	Mepolizumab 100 mg SC	Mepolizumab 75 mg IV	Placebo	Mepolizumab 100 mg SC	Placebo
ITT, n (%)	**194 (100)**	**191 (100)**	**191 (100)**	**69 (100)**	**66 (100)**
Entered Open-Label Extension (MEA115661), n (%)	176 (91)	171 (92)	175 (90)	65 (94)	61 (92)

ITT = intention-to-treat; IV = intravenous; SC = subcutaneous.
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

Exposure

[redacted].

Safety

A total of 558 (86%) patients reported an AE during the 52-week open-label extension. The most common AEs were nasopharyngitis (30%), upper respiratory tract infections (16%), and headache (14%). Serious adverse events (SAEs) were reported in 14% of patients, and the most common SAE was asthma (6%). Few patients withdrew due to an AE (2%), and there were no deaths during the extension.

Injection-site reactions occurred in 4% of patients. The incidence of systemic allergic reactions and serious infection was low (2%), and cardiovascular events and malignancies were reported in < 1% of patients.

TABLE 25: HARMS IN MEA115661

	Mepolizumab 100 mg SC (N = 651)
AEs	
Patients With > 0 AEs, n (%)	558 (86)
Common AEs (≥ 7%), n (%)	
Nasopharyngitis	196 (30)
URTI	101 (16)
Headache	88 (14)
Asthma	90 (14)
Bronchitis	80 (12)
Sinusitis	66 (10)
SAEs	
Patients With > 0 SAEs, n (%)	94 (14)
Common SAEs, n (%)	
Asthma	38 (6)
WDAEs	
WDAEs, n (%)	11 (2)
Deaths	
Deaths, n (%)	0
Notable Harms, n (%)	
Injection-site reaction	29 (4)
Systemic allergic reactions	[redacted]
Serious infection	[redacted]
Cardiovascular event	[redacted]
Malignancy	[redacted]

AE = adverse event; SAE = serious adverse event; SC = subcutaneous; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.
Source: MEA115661 Clinical Study Report.[79]

Efficacy

A total of 311 (48%) patients experienced 654 exacerbations during the 52-week extension, with an estimated exacerbation rate of 0.93 per year (95% confidence interval [CI] 0.83 to 1.04). Fifty-nine patients (9%) experienced an exacerbation requiring hospitalization or emergency department visit. Thirty-nine patients (6%) experienced an exacerbation that required hospitalization.

In patients previously treated with mepolizumab in MENSA and SIRIUS, pre-bronchodilator FEV_1 values decreased by a mean of 13 mL (SD = 374) from baseline at week 52. In patients previously treated with placebo in MENSA and SIRIUS, pre-bronchodilator FEV_1 values improved from baseline to week 52 by a mean of 100 mL (SD = 448). There was no change from baseline in ACQ-5 score in patients previously treated with mepolizumab (median change 0), while there was an improvement in ACQ-5 score in patients previously treated with placebo (median change –0.20 [range, –3.8 to 2.6]).

TABLE 26: EXACERBATIONS IN MEA115661

	Mepolizumab 100 mg SC (N = 651)
All Exacerbations	
Number of patients, n (%)	311 (48)
Number of exacerbations	654
Estimated rate/year (95% CI)	0.93 (0.83 to 1.04)
Exacerbations Requiring Hospitalization or ED Visit	
Number of patients, n (%)	59 (9)
Number of exacerbations	95
Exacerbations Requiring Hospitalization	
Number of patients, n (%)	39 (6)
Number of exacerbations	65

CI = confidence interval; ED = emergency department; SC = subcutaneous.
Source: MEA115661 Clinical Study Report.[79]

TABLE 27: LUNG FUNCTION AND ACQ-5 OUTCOMES IN MEA115661

	Mepolizumab 100 mg SC (N = 651)	
	Previously Mepolizumab	Previously Placebo
Pre-bronchodilator FEV_1, mL		
n	412	237
Baseline mean (SD)	2,010 (733)	1,957 (668)
n at week 52	379	223
Mean change from baseline at week 52 (SD)	–13 (374)	100 (448)
ACQ-5 Score		
n	390	220
Baseline mean (SD)	1.25 (1.10)	1.76 (1.13)
n at week 52	350	206
Mean change from baseline at week 52 (SD)	0.04 (0.97)	–0.30 (1.00)
Median change from baseline at week 52 (range)	0 (–4.0 to 4.0)	–0.20 (–3.8 to 2.6)

ACQ-5 = Asthma Control Questionnaire 5; FEV_1 = forced expiratory volume in 1 second; SC = subcutaneous; SD = standard deviation.
Source: MEA115661 Clinical Study Report.[39]

Conclusion

MEA115661 is an ongoing open-label extension study of MENSA and SIRIUS to evaluate the long-term safety of mepolizumab 100 mg SC in patients with severe asthma with a history of or current eosinophilic inflammation. The safety profile in the extension study was similar to what was reported in the MENSA and SIRIUS studies, with the most common AEs being nasopharyngitis and headache. No patients died during the extension and the incidences of injection-site reactions, systemic allergic reactions, serious infections, cardiovascular events, and malignancies were low. With regard to efficacy, the exacerbation rate, pre-bronchodilator FEV_1, and ACQ-5 scores remained constant in patients previously treated with mepolizumab and improved in patients previously treated with placebo. Limitations of this study included its open-label design with no control group and the enrolment of a select population that opted to continue treatment from MENSA and SIRIUS.

APPENDIX 7: SUMMARY OF DREAM (MEA112997) AND LONG-TERM EXTENSION STUDY (MEA115666)

Aim

To summarize the 52-week phase 2b/3 DREAM (MEA112997) study and its long-term extension study (MEA115666).[28] The DREAM study was not included in the systematic review as only intravenous (IV) formulations of mepolizumab were used instead of the Health Canada–approved subcutaneous (SC) formulation that is being reviewed.

Findings

DREAM (N = 616) was an international, 52-week, randomized, double-blind, placebo-controlled study that assessed the efficacy and safety of IV mepolizumab 75 mg, 250 mg, and 750 mg administered every four weeks. The primary efficacy end point was the frequency of clinically significant exacerbations as defined in MENSA and SIRIUS. The primary comparison was a linear test for a trend of a decrease in exacerbation rate with increasing dose of mepolizumab (placebo assigned a dose of 0) to check for significance at the two-sided 5% level, before comparing mepolizumab to placebo using a one-sided Hochberg testing procedure with a one-sided 2.5% level.

Secondary efficacy end points were controlled for multiplicity using the one-sided Hochberg testing procedure at the one-sided 2.5% level in the following order:

- Mean change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at week 52
- Mean change from baseline in Asthma Quality of Life Questionnaire score at week 52
- Rate of exacerbations requiring hospitalizations or emergency department visits
- Mean change from baseline in Asthma Control Questionnaire 6 (ACQ-6) score at week 52

Other end points that were not part of a testing hierarchy included:

- Time to first clinically significant exacerbation
- Time to first exacerbation requiring hospitalization or emergency department visit
- Mean change from baseline in morning peak expiratory flow (PEF)
- Mean number of days with oral corticosteroid (OCS)
- Mean change from baseline in daily salbutamol/albuterol use
- Mean change from baseline in nighttime awakening due to asthma symptoms requiring rescue medication.

Patients who completed DREAM had the option of participating in an open-label, long-term extension study (MEA115666) after experiencing a gap of ≥ 10 months after their last double-blind study medication in DREAM. In MEA115666 (N = [redacted]), patients were treated with mepolizumab 100 mg SC and were to continue receiving mepolizumab SC injections until withdrawal, discontinuation of mepolizumab development by the manufacturer, discontinuation of the study, or mepolizumab becoming commercially available. Efficacy assessments included the annualized rate of exacerbations, ACQ-5 scores, and FEV_1. At the latest cut-off date in the interim report, patients had been treated for a mean of 378 days.

Inclusion and Exclusion Criteria

Patients were to be ≥ 12 years of age and ≥ 45 kg in weight with clinical features of severe refractory asthma for ≥ 12 months before visit 1 (pre-bronchodilator FEV_1 < 80% predicted or peak flow diurnal variability > 20% on ≥ 3 days during run-in; airway reversibility FEV_1 ≥ 12% and 200 mL in past 12 months; airway hyperresponsiveness) and a confirmed history of ≥ 2 asthma exacerbations requiring treatment with systemic corticosteroids in past 12 months despite maintenance treatment with ICS plus an additional controller. Patients with likely eosinophilic airway inflammation as indicated by one of the following measures in the past 12 months: blood eosinophil level ≥ 300 cells/mcL; sputum eosinophils ≥ 3%; exhaled nitric oxide ≥ 50 ppb; prompt deterioration of asthma controlled followed by a ≤ 25% reduction in regular maintenance dose of inhaled corticosteroid (ICS) or OCS. Patients were to be on regular treatment with high-dose ICS (≥ 880 mcg/day fluticasone propionate or equivalent) with or without maintenance OCS in the 12 months before visit 1 and an additional controller medication.

Patients were excluded from DREAM if they were current smokers or had a smoking history of ≥ 10 pack-years, a clinically important lung condition other than asthma, a diagnosis of malignancy, unstable liver disease, or received omalizumab within 130 days of visit 1.

Intervention and Concomitant Medications

Patients were randomized to receive mepolizumab at doses of 75 mg, 250 mg, or 750 mg or placebo IV once every four weeks. Each vial of mepolizumab was reconstituted with 5.0 mL of sterile water for injection, making approximately 50 mg/mL of mepolizumab.

Additional asthma medications such as theophyllines or anti-leukotrienes were permitted provided they had been taken regularly in the 12 months before randomization. Maintenance OCS were permitted if at least one exacerbation in the past 12 months had occurred while on OCS and had been treated with a greater than or equal to twofold increase in the OCS dose.

Approximately 98% of patients were on ICS during the treatment period, with 51% of patients on a combination of fluticasone and salmeterol. Concomitant medications were balanced across treatment groups.

The majority of patients received all 12 doses of study medication, with no imbalances between groups.

Sample Size Calculation and Patient Disposition

A total of 128 patients per group completing the study gave 90% power to detect a decrease in the exacerbation rate with increasing dose of IV mepolizumab from 1.5/year on placebo to 0.9/year on 750 mg mepolizumab at a two-sided 5% significance level. Assuming a withdrawal rate of 15%, the planned number of randomized patients was 151 per group.

A total of 616 patients were randomized in this study, with 152 to 156 patients per treatment group. Approximately 16% of patients withdrew from the study, with the most common reason for discontinuation being an AE, lack of efficacy, or withdrawal of consent. Withdrawals were generally balanced across groups.

TABLE 28: PATIENT DISPOSITION IN DREAM

	MEP 75 mg IV	MEP 250 mg IV	MEP 750 mg IV	Placebo
Enrolled, N	888			
Run-In, N	720			
Randomized, N (%)	616			
	153 (100)	152 (100)	156 (100)	155 (100)
Discontinued, n (%)	24 (16)	21 (14)	23 (15)	28 (18)
Adverse event	5 (3)	8 (5)	9 (6)	6 (4)
Lack of efficacy	6 (4)	4 (3)	4 (3)	8 (5)
Withdrew consent	8 (5)	2 (1)	7 (4)	11 (7)
Enrolled in MEA115666, n (%)	84 (55)	90 (59)	96 (62)	77 (50)
ITT, N	153 (100)	152 (100)	156 (100)	155 (100)
PP, N	147 (96)	142 (93)	151 (97)	151 (97)
Safety, N	153 (100)	152 (100)	156 (100)	155 (100)

ITT = intention-to-treat; IV = intravenous; MEP = mepolizumab; PP = per-protocol.
Source: DREAM Clinical Study Report.[80]

Baseline Characteristics

The mean age of patients enrolled was approximately 50 years, and the majority of patients (> 60%) were female and white (90%). Almost all patients had at least two exacerbations in the past 12 months as per inclusion criteria, and the majority of patients (about 60%) exhibited elevated blood eosinophils in the past 12 months. Demographics and asthma characteristics were balanced across treatment groups.

TABLE 29: SUMMARY OF BASELINE CHARACTERISTICS

	MEP 75 mg IV (N = 153)	MEP 250 mg IV (N = 152)	MEP 750 mg IV (N = 156)	Placebo (N = 155)
Demographics				
Age (years), mean (SD)	50.2 (10.8)	49.4 (11.6)	48.6 (11.1)	46.4 (11.3)
Female, n (%)	104 (68)	93 (61)	93 (60)	97 (63)
White, n (%)	139 (91)	135 (89)	140 (90)	140 (90)
Asian, n (%)	9 (6)	7 (5)	10 (6)	8 (5)
Number of Exacerbations in Past 12 Months, n (%)				
1	0	1 (< 1)	0	1 (< 1)
2	70 (46)	74 (49)	75 (48)	65 (42)
> 2	83 (54)	77 (51)	81 (52)	89 (57)
Asthma Characteristics in Past 12 Months, n (%)				
High-dose ICS	153 (100)	152 (100)	156 (100)	155 (100)
Controller medication	153 (100)	152 (100)	156 (100)	155 (100)
SABA usage	132 (86)	129 (85)	140 (90)	136 (88)
Oral steroid bursts	66 (43)	70 (46)	82 (53)	77 (50)
Continuous OCS	48 (31)	54 (36)	50 (32)	50 (32)
Airway Inflammation Characteristics in Past 12 Months or at Visit 1, n (%)				
Blood eosinophils	85 (56)	93 (61)	91 (58)	96 (62)

	MEP 75 mg IV (N = 153)	MEP 250 mg IV (N = 152)	MEP 750 mg IV (N = 156)	Placebo (N = 155)
Sputum eosinophils	18 (12)	16 (11)	14 (9)	16 (10)
Exhaled nitric oxide	61 (40)	57 (38)	74 (47)	70 (45)
Lack of asthma control	46 (30)	41 (27)	47 (30)	48 (31)
Lung Function at Screening				
Pre-bronchodilator FEV_1 (L), mean (SD)	1.75 (0.59)	1.80 (0.63)	1.87 (0.68)	1.85 (0.69)
% predicted normal, mean (SD)	58.0 (15.9)	57.5 (15.5)	57.9 (15.9)	57.5 (16.0)
Post-bronchodilator FEV_1 (L), mean (SD)	2.10 (0.68)	2.20 (0.73)	2.27 (0.75)	2.30 (0.78)
% predicted normal, mean (SD)	70.0 (18.8)	70.3 (16.9)	70.4 (17.2)	71.4 (17.8)
Reversibility (%), mean (SD)	22.6 (20.7)	25.6 (21.8)	23.9 (19.1)	26.8 (25.0)
Reversibility (mL), mean (SD)	357 (296)	416 (312)	396 (282)	438 (317)

FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; IV = intravenous; MEP = mepolizumab; OCS = oral corticosteroids; SABA = short-acting beta agonist; SD = standard deviation.
Source: MENSA Clinical Study Report,[1] SIRIUS Clinical Study Report.[2]

Efficacy

Results for the primary and secondary end points in DREAM are presented in Table 30. The frequency of clinically significant exacerbations was statistically significantly reduced in all mepolizumab groups compared with placebo ($P < 0.001$). The linear contrast test for trend was also statistically significant, due mainly to the reduction in the rate of exacerbations in all three mepolizumab treatment groups compared with placebo and not a dose-response. Several pre-specified subgroup analyses were performed. When analyzed by baseline blood eosinophil level, there was a statistically significant interaction between baseline blood eosinophil group and treatment group ($P = 0.002$) (Figure 4). No statistically significant interaction was seen between baseline sputum eosinophil levels and treatment group, though the number of patients in this analysis was small.

For the secondary end points, statistical testing was not permissible for end points that fell below the change from baseline in pre-bronchodilator FEV_1 at week 52 because this end point had a non-significant linear trend test ($P = 0.243$). The frequency of exacerbations requiring hospitalization or emergency department visits was reduced in all mepolizumab groups compared with placebo (rate ratio 0.40 to 0.52). The frequency of exacerbations requiring hospitalization was also reduced in all mepolizumab groups compared with placebo (rate ratio 0.37 to 0.65).

Pre-bronchodilator FEV_1 at week 52 increased by 61 mL (95% confidence interval [CI], –39 to 161), 81 mL (95% CI, –19 to 180), and 56 mL (95% CI, –43 to 155) over placebo in the mepolizumab 75 mg, 250 mg, and 750 mg groups, respectively.

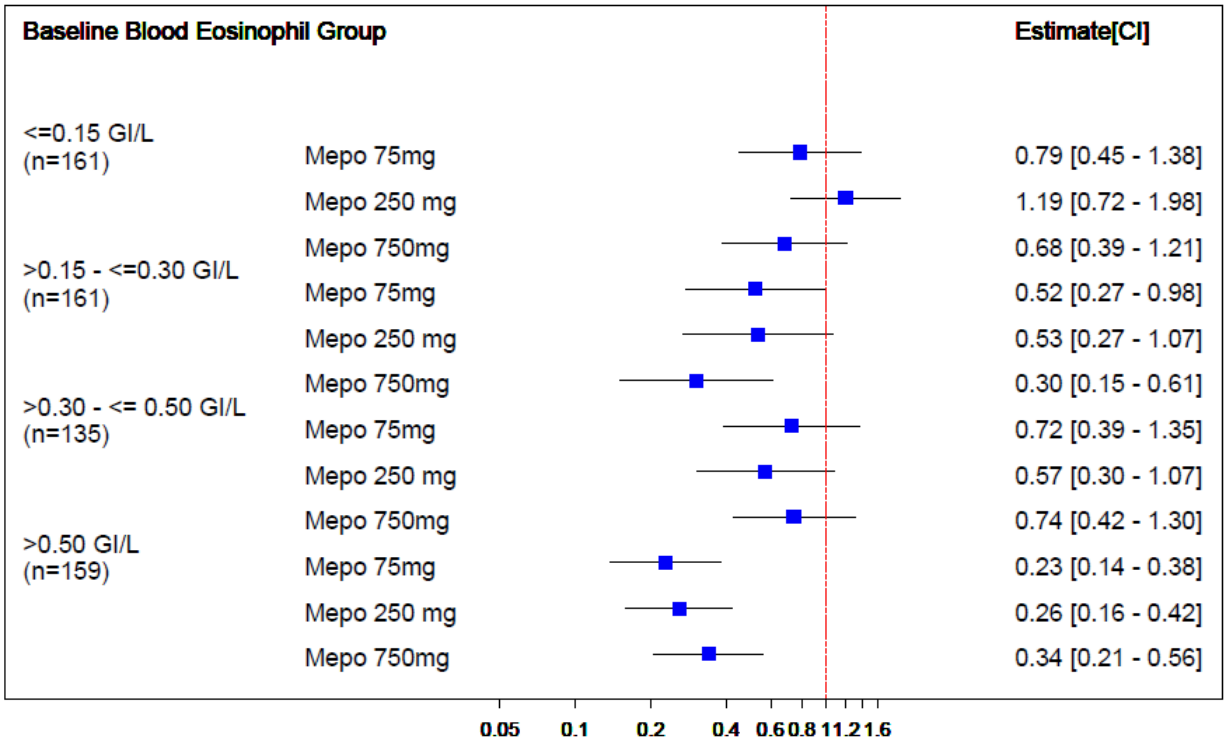
The mepolizumab groups all showed a numerical improvement (decrease) over placebo in ACQ score after 52 weeks: –0.16 (95% CI, –0.39 to 0.07), –0.27 (95% CI, –0.51 to –0.04), and –0.20 (95% CI, –0.43 to 0.03) for mepolizumab 75 mg, 250 mg, and 750 mg, respectively.

The mepolizumab groups also all showed a small improvement (increase) over placebo in Asthma Quality of Life Questionnaire score after 52 weeks: 0.08 (95% CI, –0.16 to 0.32), 0.05 (95% CI, –0.19 to

0.29), and 0.22 (95% CI, –0.02 to 0.46) for mepolizumab 75 mg, 250 mg, and 750 mg, respectively. The MCID for Asthma Quality of Life Questionnaire is 0.5 points.

The mean change from baseline in daily rescue medication use, in nighttime awakening due to asthma symptoms requiring rescue medication use, and in morning PEF were summarized by four-week periods (Table 31). For the mean change from baseline in daily rescue medication use and nighttime awakening due to asthma symptoms requiring rescue medication use at weeks 49 to 52, there were small decreases from baseline in all treatment groups. For the change from baseline in morning PEF at weeks 49 to 52, there were small increases from baseline in all treatment groups.

FIGURE 4: RATE OF CLINICALLY SIGNIFICANT EXACERBATIONS BY BASELINE BLOOD EOSINOPHIL GROUP



CI = confidence interval; Mepo = mepolizumab.
Source: DREAM Clinical Study Report.[80]

TABLE 30: PRIMARY AND SECONDARY END POINTS IN DREAM

	MEP 75 mg IV (N = 153)	MEP 250 mg IV (N = 152)	MEP 750 mg IV (N = 156)	Placebo (N = 155)
Rate of Clinically Significant Exacerbations at Week 52				
Exacerbation rate/year	1.24	1.46	1.15	2.40
P value for linear test for trend	< 0.001			
Rate ratio versus placebo (95% CI), *P* value	0.52 (0.39 to 0.69), *P* < 0.001	0.61 (0.46 to 0.81), *P* < 0.001	0.48 (0.36 to 0.64), *P* < 0.001	–
Probability of an exacerbation by week 52, % (95% CI)	48.5	58.3	50.1	69.7
Time to exacerbation, HR (95% CI)	0.45 (0.33 to 0.61)	0.60 (0.45 to 0.80)	0.46 (0.34 to 0.63)	–

	MEP 75 mg IV (N = 153)	MEP 250 mg IV (N = 152)	MEP 750 mg IV (N = 156)	Placebo (N = 155)
Rate of Exacerbations Requiring Hospitalization or ED Visits at Week 52				
Exacerbation rate/year	0.17	0.25	0.22	0.43
Rate ratio versus placebo (95% CI)	0.40 (0.19 to 0.81)	0.58 (0.30 to 1.12)	0.52 (0.27 to 1.02)	–
Probability of an exacerbation by week 52, % (95% CI)	10.4	15.9	12.4	18.5
Time to exacerbation, HR (95% CI)	0.53 (0.28 to 0.99)	0.91 (0.52 to 1.58)	0.61 (0.33 to 1.10)	–
Rate of Exacerbations Requiring Hospitalization at Week 52				
Exacerbation rate/year	0.11	0.12	0.07	0.18
Rate ratio versus placebo (95% CI)	0.61 (0.28 to 1.33)	0.65 (0.31 to 1.39)	0.37 (0.16 to 0.88)	–
Probability of an exacerbation by week 52, % (95% CI)	8.4	11.1	6.2	11.8
Time to exacerbation, HR (95% CI)	0.69 (0.33 to 1.44)	0.99 (0.50 to 1.97)	0.49 (0.22 to 1.11)	–
Pre-bronchodilator FEV_1 at Week 52, mL				
Baseline mean (SD)	1,808 (637)	1,854 (672)	1,950 (674)	1,899 (653)
N	129	129	132	127
LS mean (SE)	2,003 (38)	2,022 (37)	1,997 (37)	1,942 (38)
LS mean change (SE)	121 (38)	140 (37)	115 (37)	60 (38)
Difference (95% CI)	61 (–39 to 161)	81 (–19 to 180)	56 (–43 to 155)	
ACQ Score at Week 52, Ml				
Baseline mean (SD)	2.2 (1.1)	2.4 (1.1)	2.3 (1.2)	2.5 (1.1)
N	127	126	129	121
LS mean (SE)	1.56 (0.09)	1.45 (0.09)	1.52 (0.09)	1.72 (0.09)
LS mean change (SE)	–0.75 (0.09)	–0.87 (0.09)	–0.80 (0.09)	–0.59 (0.09)
Difference (95% CI)	–0.16 (–0.39 to 0.07)	–0.27 (–0.51 to –0.04)	–0.20 (–0.43 to 0.03)	–
AQLQ Score at Week 52, mL				
Baseline mean (SD)				
N	128	127	129	123
LS mean (SE)	5.00 (0.09)	4.97 (0.09)	5.14 (0.09)	4.92 (0.09)
LS mean change (SE)	0.80 (0.09)	0.77 (0.09)	0.93 (0.09)	0.71 (0.09)
Difference (95% CI)	0.08 (–0.16 to 0.32)	0.05 (–0.19 to 0.29)	0.22 (–0.02 to 0.46)	–

AQLQ = Asthma Quality of Life Questionnaire; ACQ = Asthma Control Questionnaire; CI = confidence interval; ED = emergency department; FEV_1 = forced expiratory volume in 1 second; HR = hazard ratio; IV = intravenous; LS = least squares; MEP = mepolizumab; SD = standard deviation; SE = standard error.
Source: DREAM Clinical Study Report.[80]

TABLE 31: OTHER EFFICACY END POINTS IN DREAM

	MEP 75 mg IV (N = 153)	MEP 250 mg IV (N = 152)	MEP 750 mg IV (N = 156)	Placebo (N = 155)
Daily Rescue Medication Use at Weeks 49 to 52 (occasions/day)				
Baseline mean (SD)				
N	132	132	133	128
LS mean (SE)	1.99 (0.17)	1.79 (0.17)	2.04 (0.17)	2.13 (0.17)
LS mean change (SE)	–0.63 (0.17)	–0.83 (0.17)	–0.58 (0.17)	–0.49 (0.17)
Difference (95% CI), *P* value[a]	–0.15 (–0.60 to 0.31)	–0.34 (–0.79 to 0.11)	–0.09 (–0.54 to 0.36)	–
Nighttime Awakenings Due to Asthma Symptoms Requiring Rescue Medication at Weeks 49 to 52				
Baseline mean (SD)				
N	132	132	133	128
LS mean (SE)	0.53 (0.08)	0.60 (0.07)	0.51 (0.07)	0.62 (0.08)
LS mean change (SE)	–0.46 (0.08)	–0.40 (0.07)	–0.48 (0.07)	–0.37 (0.08)
Difference (95% CI), *P* value[a]	–0.09 (–0.30 to 0.11)	–0.03 (–0.23 to 0.17)	–0.11 (–0.31 to 0.09)	–
Morning PEF at Weeks 49 to 52, L/min				
Baseline mean (SD)				
N	132	132	133	128
LS mean (SE)	281.1 (5.6)	288.1 (5.5)	287.7 (5.5)	277.9 (5.6)
LS mean change (SE)	9.5 (5.6)	16.4 (5.5)	16.1 (5.5)	6.3 (5.6)
Difference (95% CI), *P* value[a]	3.2 (–11.8 to 18.2)	10.1 (–4.8 to 25.1)	9.8 (–5.1 to 24.7)	–

CI = confidence interval; IV = intravenous; LS = least squares; MEP = mepolizumab; PEF = peak expiratory flow; SD = standard deviation; SE = standard error.
[a] Information was collected on a daily basis from the eDiary and averaged over 4-week periods.
Source: DREAM Clinical Study Report.[80]

Safety

Approximately 80% of patients reported at least one adverse event (AE) during the DREAM study. AEs were generally balanced across treatment groups. The most common AEs included headache and nasopharyngitis. Serious adverse events (SAEs) were reported in 14% of patients in the mepolizumab 75 mg IV group to 17% of patients in the placebo group. The most common SAE was asthma. Withdrawals due to adverse events (WDAEs) ranged from 3% to 6% across treatment groups. There were two deaths in the mepolizumab 250 mg IV group and one death in the mepolizumab 750 mg IV group. Infusion-related reactions were higher in the mepolizumab 750 mg IV group (12%) compared with the other mepolizumab groups (5% to 8%) and the placebo group (6%). Serious infections, cardiac disorders, and malignancies were low across all treatment groups.

TABLE 32: HARMS IN DREAM

	MEP 75 mg IV (N = 153)	MEP 250 mg IV (N = 152)	MEP 750 mg IV (N = 156)	Placebo (N = 155)
AEs				
Patients With > 0 AEs, n (%)	126 (82)	126 (83)	122 (78)	121 (78)
Common AEs (≥ 10% Patients), n (%)				
Headache	32 (21)	32 (21)	32 (21)	27 (17)
Nasopharyngitis	34 (22)	33 (22)	29 (19)	24 (15)
Asthma	14 (9)	26 (17)	16 (10)	24 (15)
Sinusitis	10 (7)	10 (7)	12 (8)	16 (10)
URTI	10 (7)	10 (7)	12 (8)	16 (10)
Bronchitis	17 (11)	13 (9)	13 (8)	15 (10)
Back pain	11 (7)	7 (5)	15 (10)	11 (7)
Infusion-related reaction	8 (5)	12 (8)	19 (12)	10 (6)
SAEs				
Patients With > 0 SAEs, n (%)	22 (14)	25 (16)	21 (13)	27 (17)
Common SAEs, n (%)				
Asthma	11 (7)	16 (11)	9 (6)	17 (11)
WDAEs				
WDAEs, n (%)	5 (3)	8 (5)	9 (6)	6 (4)
Deaths				
Deaths, n (%)	0	2 (1)	1 (< 1)	0
Notable Harms, n (%)				
Infusion-related reaction	8 (5)	12 (8)	19 (12)	10 (6)
Serious infection	7 (5)	3 (2)	5 (3)	5 (3)
Cardiac disorder	2 (1)	1 (< 1)	4 (3)	1 (< 1)
Malignancy	1 (< 1)	1 (< 1)	0	0

AE = adverse event; IV = intravenous; MEP = mepolizumab; SAE = serious adverse event; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.
Source: DREAM Clinical Study Report.[80]

Long-Term Extension (MEA115666)

Of the [redacted] patients enrolled from DREAM, [redacted] patients were treated during the long-term extension with mepolizumab 100 mg SC after [redacted] months. The mean age was [redacted] years, with [redacted] of patients being female and [redacted] being white. The mean (standard deviation [SD]) time since completion of DREAM was [redacted] months. The mean number of exacerbations during this period of no mepolizumab treatment was [redacted] exacerbations per patient. At the data cut-off, patients had received treatment for a mean of [redacted].

During the long-term extension period, [redacted] of patients reported at least one AE, with the most common AEs being [redacted] and [redacted]. [redacted] patients reported an SAE, with the most common one being [redacted]. [redacted] withdrew due to an AE and [redacted] died. Injection-site reactions were reported in [redacted] patients, serious infections were reported in [redacted] patients, cardiovascular events were reported in [redacted] patients, and malignancies were reported in [redacted] patients.

During the long-term extension period, a total of [redacted] patients experienced [redacted] exacerbations, with an estimated annual rate of [redacted], compared with an annual rate [redacted] before the start of study. There were [redacted] patients [redacted] who experienced [redacted] exacerbations requiring hospitalization or an emergency department visit compared with [redacted] patients [redacted] patients between studies. There were [redacted] patients [redacted] that experienced [redacted] exacerbations requiring hospitalization after treatment initiation compared with [redacted] patients [redacted] between the studies.

TABLE 33: HARMS IN MEA115666

	MEP 100 mg SC (N = [redacted])
AEs	
Patients With > 0 AEs, n (%)	[redacted]
Common AEs (≥ 10% Patients), n (%)	
Headache	[redacted]
URTI	[redacted]
Asthma	[redacted]
Arthralgia	[redacted]
Back pain	[redacted]
Bronchitis	[redacted]
SAEs	
Patients With > 0 SAEs, n (%)	[redacted]
Common SAEs, n (%)	
Asthma	[redacted]
WDAEs	
WDAEs, n (%)	[redacted]
Deaths	
Deaths, n (%)	[redacted]
Notable Harms, n (%)	
Injection-site reaction	[redacted]
Serious infection	[redacted]
Cardiovascular event	[redacted]
Malignancy	[redacted]

AE = adverse event; MEP = mepolizumab; SAE = serious adverse event; SC = subcutaneous; URTI = upper respiratory tract infection; WDAE = withdrawal due to adverse event.
Source: MEA115666 Clinical Study Report.[38]

TABLE 34: EXACERBATIONS IN MEA115666

	MEP 100 mg SC (N = [redacted])
All Exacerbations	
Number of patients, n (%)	[redacted]
Number of exacerbations	[redacted]
Estimated rate/year (95% CI)	[redacted]
Exacerbations Requiring Hospitalization or ED Visit	
Number of patients, n (%)	[redacted]
Number of exacerbations	[redacted]
Exacerbations Requiring Hospitalization	
Number of patients, n (%)	[redacted]
Number of exacerbations	[redacted]

CI = confidence interval; ED = emergency department; MEP = mepolizumab; SC = subcutaneous.

Conclusion

DREAM (N = 616) was an international, 52-week, randomized, double-blind, placebo-controlled study that assessed the efficacy and safety of IV mepolizumab 75 mg, 250 mg, and 750 mg administered every four weeks. Results from DREAM suggested that mepolizumab IV at doses of 75 mg, 250 mg, and 750 mg reduced the frequency of clinically significant exacerbations compared with placebo. The population that was enrolled met at least one of the following criteria in the past 12 months: blood eosinophils ≥ 300 cells/mcL; sputum eosinophils ≥ 3%; exhaled nitric oxide level ≥ 50 ppb; or rapid deterioration of asthma control following a ≤ 25% reduction in steroids. These criteria differed from MENSA and SIRIUS in that they looked at sputum eosinophils and exhaled nitric oxide levels, but did not include a criterion for ≥ 150 cells/mcL at screening. However, it appears that these parameters were able to identify a target population that is responsive to mepolizumab IV. Overall, mepolizumab IV 75 mg, 250 mg, and 750 mg were well tolerated in this population of patients with severe eosinophilic asthma that was not controlled on a combination of ICS and additional controller.

APPENDIX 8: SUMMARY OF INDIRECT COMPARISONS

The manufacturer conducted an indirect treatment comparison (ITC) based on a systematic review[81] to evaluate the relative efficacy of mepolizumab and omalizumab in the treatment of patients with severe asthma who could be eligible to receive either mepolizumab or omalizumab therapy. The ITC was conducted because there are no head-to-head randomized controlled trials directly comparing mepolizumab and other drug therapies for severe asthma, including omalizumab. The primary objective was to assess the relative efficacy and safety of mepolizumab versus omalizumab as add-on therapy to standard of care in the treatment of adults and adolescents (≥ 12 years old) with severe asthma, in terms of exacerbations, hospitalization due to exacerbation, forced expiratory flow in one second (FEV_1), and safety profile (adverse events [AEs], serious adverse events [SAEs], withdrawal due to adverse events [WDAEs]). The following is a summary and critical appraisal of the methods and main findings of the ITC.

Summary of Indirect Treatment Comparison

Methods

Eligibility Criteria: A systematic literature search included both electronic and manual components. The electronic search was mainly performed in MEDLINE (via PubMed), EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Health Technology Assessments Database (HTA), and PASCAL, with no limits applied for all databases. Study selection was accomplished by two researchers independently through two levels of study screening. Data were extracted by one investigator and verified by a second reviewer. All included randomized controlled trials were evaluated by a single researcher for validity with the quality assessment criteria adopted from the guidance for evidence submission published by The National Institute for Health and Care Excellence (NICE 2012). The main inclusion criteria for the systematic review were severe asthma patients ≥ 12 years receiving ≥ 1,000 mcg/day beclomethasone dipropionate-equivalent inhaled corticosteroid [ICS] plus ≥ 1 additional controller, and a documented history of exacerbations.

The interventions of interest were mepolizumab 100 mg subcutaneous [SC] and omalizumab doses compatible with a Health Canada–approved dose regimen (such as 150 mg to 375 mg SC every two or four weeks), both in combination with standard of care. Studies or treatment groups that included mepolizumab 75 mg intravenous [IV] as an intervention are not reported in this summary because this dosing regimen is not approved by Health Canada and is out of scope for this review. The comparators of interest included placebo in double-blind randomized controlled trials or control in the open-label randomized controlled trials, also in combination with standard of care. The main outcomes of interest included clinically significant exacerbations, defined as requiring oral or systemic corticosteroids (or at least a doubling of existing dose for maintenance oral corticosteroid [OCS] patients); exacerbation requiring hospitalization (also known as hospitalization due to exacerbation); FEV_1 % predicted; and safety outcomes (including AEs, SAEs and WDAEs).

Indirect Treatment Comparison: The manufacturer reported it was unable to identify and analyze data for a true severe asthma “overlap” population — that is, patients eligible to receive either mepolizumab or omalizumab therapy — from the identified studies, and therefore three approximated ITC populations were analyzed. ITC population 1 was an approximation of the patient population, defined based on ≥ 2 exacerbations or ≥ 1 severe exacerbation resulting in hospitalization in the previous 12 months. ITC population 2 included patients from studies with ≥ 1 exacerbation in the previous 12 months. ITC population 3 comprised all patients eligible for SC mepolizumab from the mepolizumab

randomized controlled trials (i.e., regardless of their eligibility for omalizumab). The manufacturer noted that "the design and conduct of this [ITC population] study was before receiving the notice of compliance from Health Canada. Therefore, the name and definition of ITC population 3 is not exactly representative of the mepolizumab indication population in Canada." The findings for ITC population 3, therefore, were not summarized in detail because the relevance of this population to the review is uncertain.

The ITC main outcomes were clinically significant exacerbation rate, hospitalization due to exacerbation, mean change in FEV_1, and the safety outcomes including AEs, SAES, and WDAEs. Analysis of the available dataset for each ITC was conducted using the Bucher method. A random-effects model was selected as the choice of method to synthesize individual study results in order to account for any potential unexplained imbalanced between the studies.

For rate data — e.g., for exacerbation rates — the combined exacerbation rate ratio for each treatment was estimated from individual studies. For continuous data — e.g., mean change in FEV_1 — the combined mean difference in change from baseline for each treatment was estimated from individual studies. For binary outcomes (yes or no) — e.g., safety data — the odds ratios (ORs) for each treatment of interest relative to a common comparator were estimated using standard meta-analyses as proposed by the Mantel–Haenszel method for more than two studies or inverse-variance method for a single study. No head-to-head studies comparing mepolizumab and omalizumab were identified and included in the ITC; therefore, no analysis was done to check the inconsistency (direct versus indirect evidence) in this ITC. Missing standard deviations were imputed from one or more of the other studies. Key assumptions regarding homogeneity (I2 statistic), similarity, and consistency were assessed. Meta-regression was pre-planned to adjust for heterogeneity between studies if a sufficient number of trials was available to conduct the analysis.

Results

Study and Patient Characteristics: [redacted]

Results of the ITC Analysis

1. Population 1 Base-Case Analysis:

Clinically Significant Exacerbations

[redacted]

Hospitalization Due to Exacerbation

[redacted]

FEV_1

[redacted]

Adverse Events, Serious Adverse Events, and Withdrawal Due to Adverse Events

[redacted]

[redacted]

2. Population 2 Base-Case Analysis:

[redacted]

3. Indirect Treatment Comparison Sensitivity Analysis for Population 1 and Population 2:

[redacted]

[redacted]

4. In Indirect Treatment Comparison Population 3 "Licensed":

[redacted]

Critical Appraisal of Indirect Comparison

The quality of the manufacturer-submitted ITC was assessed according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons,[82] and commentary for each of the relevant items identified by ISPOR are provided in Table 38.

Strengths: The ITC was based on a systematic review to identify all relevant studies. Validity of all individual studies was assessed using methodology adopted from the guidance published by the Centre for Reviews and Dissemination.[83] The analysis was conducted using an appropriate and well-reported methodology (i.e., Bucher method). The outcome measures assessed in the ITC were appropriate and consistent with some of the key efficacy assessments included in the CDR clinical review.

Limitations: One of the major limitations of the ITC body of evidence was that the true "overlap" population (i.e., patients who were eligible for either mepolizumab or omalizumab) could not be confirmed due to insufficient information in the omalizumab trials. Lack of information on eosinophil levels within the omalizumab studies meant that the analyses were likely to have included patients who would not actually be eligible for mepolizumab, based on the mepolizumab trial inclusion criteria and approved indication. A post hoc subgroup analysis of the EXTRA trial (Hanania et al.[84]) reported that omalizumab may be more efficacious than placebo in patients with higher eosinophils (≥ 260 cells/mcL blood). Thus, it was likely that these ITC findings in the "approximated overlap populations" might be biased in favour of mepolizumab. The generalizability of the ITC findings based on the "approximate overlap population" to patients clinically truly indicated for either mepolizumab or omalizumab is uncertain. In addition, the rationale for including DREAM is not aligned with the Health Canada–approved indication for mepolizumab.[11]

The ITC included data on adolescents and adults (i.e., patients ≥ 12 years old). Although the pivotal study for mepolizumab, MENSA, included adolescents and adults, patients younger than 18 years comprised ≤ 5% of the study population. The Health Canada–approved mepolizumab indication is for patients ≥ 18 years old. The impact of including these patients from studies of both treatments is unclear.

Differences in findings may reflect different baseline risks or characteristics, even if the effect estimates are consistent between trials. No meta-regression analyses to adjust for factors that may bias comparisons were conducted because there were too few studies. In fact, it is uncertain how heterogeneity across studies was accounted for, other than use of random-effects modelling for the meta-analysis, where applicable.

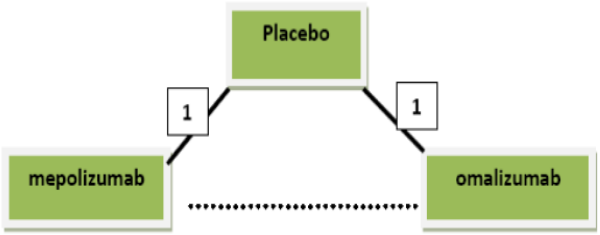
There were few studies included in the analysis, especially for mepolizumab, compounded by the restrictive inclusion criteria and the fact that only subpopulations were defined for the ITC base-case analysis. Therefore, the sparse nature of the data and likely limited power to detect a difference

between treatments means there is a high degree of uncertainty around the comparisons. Finally, there was no ITC for some other clinically important outcomes identified in this review such as use of OCS, quality of life, or days missed from work or school.

Conclusion

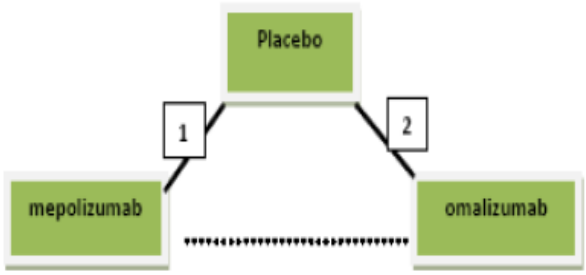
In the absence of head-to-head trial data for mepolizumab with omalizumab, the manufacturer conducted an ITC analysis based on a systematic review of randomized controlled trials to compare the efficacy and safety of mepolizumab with omalizumab in the treatment of patients with severe asthma. [redacted], there are very serious limitations with the analysis — in part stemming from the limited number of source trials for the analysis — and a high degree of uncertainty associated with the ITC findings. Therefore, no conclusion can be drawn regarding the comparative effectiveness and safety of mepolizumab with omalizumab in the treatment of severe asthma.

FIGURE 5: POPULATION 1 — BASE-CASE EVIDENCE NETWORK DIAGRAM FOR ASTHMA EXACERBATION, HOSPITALIZATION, FEV_1, AND WITHDRAWAL DUE TO ADVERSE EVENTS



FEV_1 = forced expiratory volume in 1 second.
Source: Indirect Treatment Comparison report.[81]

FIGURE 6: POPULATION 1 — BASE-CASE EVIDENCE NETWORK DIAGRAM FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

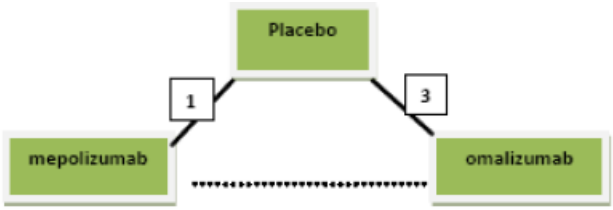


Source: Indirect Treatment Comparison report.[81]

FIGURE 7: POPULATION 2 — BASE-CASE EVIDENCE NETWORK DIAGRAM FOR ASTHMA EXACERBATION AND WITHDRAWAL DUE TO ADVERSE EVENTS

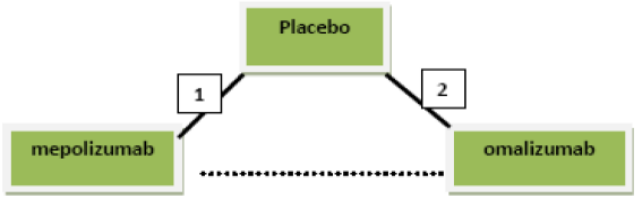
Source: Indirect Treatment Comparison report.[81]

FIGURE 8: POPULATION 2 — BASE-CASE EVIDENCE NETWORK DIAGRAM FOR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS



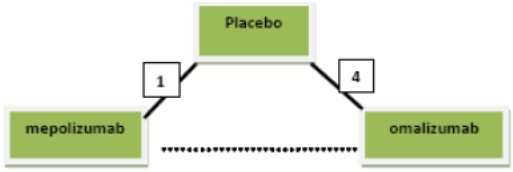
Source: Indirect Treatment Comparison report.[81]

FIGURE 9: POPULATION 1 — SENSITIVITY ANALYSIS EVIDENCE NETWORK DIAGRAM FOR ASTHMA EXACERBATION



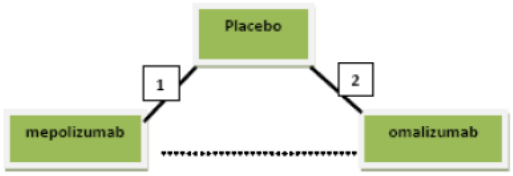
Source: Indirect Treatment Comparison report.[81]

FIGURE 10: POPULATION 2 — SENSITIVITY ANALYSIS EVIDENCE NETWORK DIAGRAM FOR ASTHMA EXACERBATION, ADVERSE EVENTS, AND SERIOUS ADVERSE EVENTS



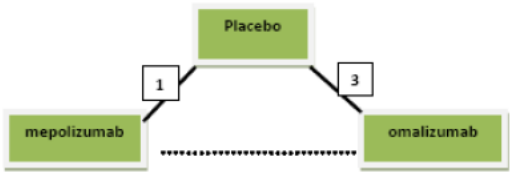
Source: Indirect Treatment Comparison report.[81]

FIGURE 11: POPULATION 2 — SENSITIVITY ANALYSIS EVIDENCE NETWORK DIAGRAM FOR HOSPITALIZATION DUE TO EXACERBATION (SAME AS POPULATION 1 BASE)



Source: Indirect Treatment Comparison report.[81]

FIGURE 12: POPULATION 2 — SENSITIVITY ANALYSIS EVIDENCE NETWORK DIAGRAM FOR WITHDRAWAL DUE TO ADVERSE EVENTS



Source: Indirect Treatment Comparison report.[81]

TABLE 35: INCLUDED STUDIES FOR EACH OUTCOMES IN POPULATION 1 AND POPULATION 2

Outcomes	MEP Studies	OMA Studies				
		DB Studies for Base Case			OL Studies Added for Sensitivity	
	For Pop 1 and Pop 2	Pop 1[a]		Pop 2	Pop 1	Pop 2
	MENSA[1]	Humbert (2005)[85]	Chanez (2010)[86]	Hanania (2011)[87]	Nivem (2008)[88]	Bousquet (2011)[89]
Exacerbation	+	+	–	+	+	+
Hospitalization	+	+	–	–	–	+
FEV_1	+	+	–	–	–	–
AEs	+	+	+	+	–	+
SAEs	+	+	+	+	–	+
Fatal AEs	+	+	+	+	–	–
WDAEs	+	+	–	+	–	+

AE = adverse event; DB = double blind; FEV_1 = forced expired volume in 1 second; ITC = indirect treatment comparison; MEP = mepolizumab; OL = open label; OMA = omalizumab; Pop = population; SAE = serious adverse event; WDAE = withdrawal due to adverse events.
Note: The "+" sign means the study was included for specific outcome analysis; the "–" sign means the study was not included in the analysis. Study DREAM,[28] included for ITC population 3, is not presented in this summary.
[a] The studies included in ITC population 1 were also included in ITC population 2. The studies included in population 1 and population 2 were also included in sensitivity analysis for population 1 and population 2 respectively.

TABLE 36: PATIENT CHARACTERISTICS IN INCLUDED STUDIES IN INDIRECT TREATMENT COMPARISON

Studies	MEP or OMA	Placebo or Control
Study on MEP		
MENSA (Canadian subanalysis only)	MEP	Placebo
N	[redacted]	[redacted]
Age, years (SD)	[redacted]	[redacted]
Male gender, n (%)	[redacted]	[redacted]
Exacerbations during the previous year (SD)	[redacted]	[redacted]
Studies on OMA		
Humbert, 2005	OMA	Placebo
N	209	210
Age, years (SD)	Mean 43 (13), range: 12 to 79	Mean 43 (14), range: 13 to 71
Gender, n (%)	68 (33)	72 (34)
FEV_1, % of predicted, (SD)	Mean 61 (14), range: 18 to 101	Mean 62 (14), range: 30 to 96
Asthma duration, years (SD)	Mean 23 (15), range: 1 to 72	Mean 23 (15), range: 1 to 66
Exacerbations in the period of 14 months (SD)	Mean 2.64 (1.56)	Mean 2.41 (1.09)
Hanania 2011	OMA	Placebo
N	427	421
Age, years (SD)	Mean 44 (14)	Mean 45 (14)
Male, n (%)	165 (39)	126 (30)
FEV_1, % of predicted, (SD)	Mean 65 (15)	Mean 65 (14)
Asthma duration, years (SD)	Mean 22.8 (15.4)	Mean 24.7 (15.8)
Exacerbations in the previous year (SD)	Mean 2 (2.2 SD)	Mean 1.9 (1.5)
Chanez 2010	OMA	Placebo
N	20	11
Age, years (SD)	Mean 46 (13), range: 23 to 74	Mean 51 (16), range: 25 to 74
Male, n (%)	6 (30)	6 (55)
FEV_1, % of predicted (SD)	Mean 61 (15), range: 35 to 79	Mean 67 (11), range: 50 to 90
Asthma duration, years (SD)	Mean 31 (19), range: 3 to 74	Mean 32 (19), range: 1 to 59
Niven 2008	OMA	Control
N	115	49
Age, years (SD)	Mean 39 (16), range 12 to 73	39 (13), range 15 to 71
Male, n (%)	29 (25)	15 (31)
FEV_1, % of predicted (SD)	Mean 66 (21)	Mean 64 (19)
Bousquet 2011	OMA + OAT, n = 272	OAT, n = 128
Age, years (SD)	Mean 47 (13)	Mean 46 (13)
Male, n (%)	89 (33)	52 (41)
FEV_1, % of predicted (SD)	Mean 63 (12)	Mean 61 (13)

AE = adverse event; FEV_1 = forced expired volume in 1 second; ITC = indirect treatment comparison; MEP = mepolizumab; OAT = optimized asthma therapy; OL = open label; OMA = omalizumab; Pop = population; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.
Note: For MENSA, only the group of mepolizumab (n = 58) in the Canada subset is presented in this table because it was in ITC.

TABLE 37: SUMMARY OF INDIRECT TREATMENT COMPARISON RESULTS

ITC Population	ITC Outcome	Mepo versus OMA	
		Base-Case Analysis (DB Study Only)	Sensitivity Analysis (by Adding Open-Label Study)
		Rate Ratio (95% CI)	
ITC Pop 1 "Overlap"[a]	Clinically significant exacerbation rate	[redacted]	[redacted]
	Hospitalization rate	[redacted]	[redacted]
		Mean Difference (95% CI)	
	Change from baseline in % predicted FEV_1	[redacted]	
		OR (95% CI)	
	Proportion of patients with any AE	[redacted]	
	Proportion of patients with any SAE	[redacted]	
	Proportion of patients WDAE	[redacted]	
		RR (95% CI)	
ITC Pop 2 "Expanded overlap"[b]	Clinically significant exacerbation rate	[redacted]	[redacted]
	Hospitalization rate	[redacted]	[redacted]
	Change from baseline in % predicted FEV_1		[redacted]
		OR (95% CI)	
	Proportion of patients with any AE	[redacted]	[redacted]
	Proportion of patients with any SAE	[redacted]	[redacted]
	Proportion of patients WDAE	[redacted]	[redacted]

AE = adverse event; CI = confidence interval; DB = double blind; FEV_1 = forced expiratory volume in 1 second; ITC = indirect treatment comparison; Mepo = mepolizumab; OMA = omalizumab; OR = odds ratio; Pop = population; RCT = randomized controlled trial; RR = rate ratio; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Note: ITC population 3 is not presented. Point estimate: rate ratio for efficacy outcomes, OR for safety outcomes, and MD for FEV_1.
[a] The primary ITC population, considered the best possible approximation, given available data, of the patient population that is eligible for both mepolizumab and omalizumab.
[b] An alternative specification that reduces the RCT exacerbation history enrolment criterion from ITC Pop 1.

TABLE 38: APPRAISAL OF NETWORK META-ANALYSIS USING ISPOR CRITERIA

ISPOR Checklist Item[82]		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting a network meta-analysis and the study objectives were clearly stated.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for individual RCT were clearly stated. • All treatments were double-blindly administered. • Information sources and search strategy were well reported. • Methods for selection process and data extraction were clearly reported. • Validity of individual studies was assessed using methodology adopted from the guidance for evidence submission published by NICE.
3.	Are the outcome measures described?	• Outcomes assessed in the network meta-analysis were clearly stated. • Justification of the outcome measures was provided.
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• A description of the statistical model was provided. • Due to lack of head-to-head trials, the report did not include a comparison of direct and indirect estimates of effect. • Analysis framework was provided for all analyses.
5.	Are sensitivity analyses presented?	• Sensitivity analysis was performed and presented. • Meta-regression sensitivity analyses were planned but not performed due to the very small number of studies meeting the ITC inclusion criteria.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• A very brief table with study and patient characteristics was provided. No detailed demographic and baseline disease characteristics were presented. • A figure showing the network of studies was provided.
7.	Does the study describe an assessment of model fit?	• Both fixed-effects and random-effects models were considered.
8.	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for each outcome measure including point estimates and 95% credible intervals as a measure of uncertainty.
9.	Sensitivity/scenario analyses	• Results of the sensitivity analyses were presented in the report

ITC = indirect treatment comparison; NICE = The National Institute for Health and Care Excellence; RCT = randomized controlled trial.

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