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Abstract

Background: We performed *post hoc* analyses to evaluate the effect of humanized monoclonal antibody mepolizumab in patients with severe eosinophilic asthma previously treated with omalizumab.

Methods: Data were collected from two randomized double-blind, placebo-controlled studies: MENSA (NCT01691521: 32-week treatment phase) and SIRIUS (NCT01691508: 24-week treatment phase). Active treatment was 75 mg intravenous mepolizumab (MENSA) or 100 mg subcutaneous mepolizumab (MENSA, SIRIUS). Patients had evidence of eosinophilic inflammation ≥150 cells/μl (at screening) or ≥300 cells/μl (during the previous year). Primary outcomes were the rate of exacerbations (MENSA) and the percentage reduction in oral corticosteroid (OCS) dose (SIRIUS). Other outcomes included lung function (forced expiratory volume in 1 s and morning peak expiratory flow), Asthma Control Questionnaire (ACQ-5), St George's Respiratory Questionnaire (SGRQ) scores, and safety.

Results: Overall, 576 patients were included from MENSA and 135 from SIRIUS, with 13% and 33% previously receiving omalizumab, respectively. In MENSA, mepolizumab reduced the rate of exacerbations by 57% (prior omalizumab) and 47% (no prior omalizumab) *vs* placebo. In SIRIUS, reductions in OCS use were comparable regardless of prior omalizumab use. Despite reducing chronic OCS use, mepolizumab also resulted in similar reductions in exacerbation rate relative to placebo in both subgroups. Asthma control and quality of life improved with mepolizumab *vs* placebo in both studies independent of prior omalizumab use, as shown by ACQ-5 and SGRQ scores. Adverse events were also comparable irrespective of prior omalizumab use.

Conclusions: These *post hoc* analyses indicate that patients with severe eosinophilic asthma respond positively to mepolizumab regardless of prior use of omalizumab.

Asthma is a common chronic inflammatory disease of the airways that affects 5–10% of adults and children and can generally be controlled with inhaled therapy (1). However, around 10% of patients with asthma suffer from severe disease, which represents a substantial burden in terms of morbidity, mortality, and economic impact (1–3).

The treatment for severe asthma is often complex, with 30–40% of patients requiring the addition of an oral corticosteroid (OCS) to achieve control (4–6). OCS use can result in serious and irreversible side-effects (6–8); consequently, patients often use lower OCS maintenance doses than those required to completely manage their symptoms. Current OCS-sparing treatments, such as other agents with general immunosuppressive properties (i.e. methotrexate and cyclosporine A), are not generally recommended for severe asthma owing to their high risk-to-low benefit ratio (3).

Recurrent asthma exacerbations are a major problem in some patients and can predominate in the subgroup of patients with asthma who have elevated eosinophils and high T-helper type 2 (Th2) inflammation (3, 9–11).

Omalizumab is a humanized monoclonal antibody that selectively binds to immunoglobulin E (IgE) and leads to downregulation of the high-affinity receptor for IgE (FcERI) at the surface of immune cells involved in severe asthma (12). Clinical study results, including those from real-life studies, have demonstrated that omalizumab is effective in the treatment for allergic asthma (13–16). Omalizumab has been available to patients with asthma for more than 10 years (17); however, it is ineffective in some patients whose asthma remains uncontrolled, and these patients subsequently discontinue this therapy.

In the United States (US), the approved FDA criteria for receiving omalizumab (every 2 or 4 weeks) include a positive skin test or *in vitro* reactivity to a perennial aeroallergen, and body weight and pretreatment IgE combinations ranging from 30 to 150 kg and 30 to 700 IU/ml, respectively. The approved EU-licensed criteria for receiving omalizumab (every 2 or 4 weeks) also include a positive skin test or *in vitro* reactivity to a perennial aeroallergen, with different ranges of body weight (20–150 kg) and pretreatment IgE levels (30–1500 IU/ml), compared with the US.

The humanized monoclonal antibody mepolizumab may be a treatment option for this patient population. This antibody binds to and neutralizes interleukin (IL)-5, a cytokine involved in the development of eosinophils in the bone marrow and also in the mobilization, persistence, and activation of eosinophils (18, 19). Clinical study results have shown that mepolizumab can reduce exacerbations and OCS use in patients with severe eosinophilic asthma (20–24). Up to 50% of patients with asthma are atopic (25, 26), so it is important to assess whether patients who are unresponsive to omalizumab respond to mepolizumab.

We performed *post hoc* analyses to evaluate the effect of mepolizumab in patients with severe eosinophilic asthma who had previously been treated with omalizumab and who had participated in one of two randomized, double-blind studies: MENSA (mepolizumab as adjunctive therapy in patients with severe asthma) (24) or SIRIUS (steroid reduction with mepolizumab study) (20). As patients in the DREAM study (22) were not asked to self-report prior omalizumab treatment, it was not possible to include data from this study in the current report. Here, we present the key efficacy and safety findings from these *post hoc* analyses.

Methods

Clinical studies

Post hoc analyses were performed using data collected from two multicenter, randomized, double-blind, placebo-controlled, parallel-group studies: MENSA (MEA115588; clinicaltrials.gov: NCT01691521) (24) and SIRIUS (MEA115575; NCT01691508) (20).

In MENSA, eligible patients had recurrent asthma exacerbations (≥2 events treated with systemic corticosteroids within the previous year). In SIRIUS, patients were eligible if they had ≥6 months of maintenance treatment with OCS prior to study start; patients were not required to have a history of exacerbations within the previous year. All patients in each study were required to have evidence of eosinophilic inflammation (an eosinophil cell count of ≥150 cells/μl at screening or ≥300 cells/μl during the previous year) (27).

All patients in MENSA received high-dose inhaled corticosteroids (ICS) plus additional controller(s), with or without an OCS. In SIRIUS, all patients had to be taking 5–35 mg oral prednisone daily, in addition to high-dose ICS and additional controller(s).

The MENSA study consisted of a 1- to 6-week run-in phase, followed by a 32-week treatment phase, then an 8-week follow-up safety phase. In the treatment phase, patients were randomized 1 : 1 : 1 to receive 75 mg intravenous (IV) mepolizumab, 100 mg subcutaneous (SC) mepolizumab, or placebo, every 4 weeks for 32 weeks.

Before randomization in the SIRIUS study, the lowest effective dose of OCS was determined for each patient (the optimization phase). Patients requiring <5 mg/day after the optimization phase were not continued in the study. Patients were then randomized 1 : 1 to receive 100 mg SC mepolizumab or placebo every 4 weeks for 24 weeks and their OCS dose was reduced between weeks 4 and 20, according to the criteria outlined in the protocol. An 8-week follow-up safety phase began at week 24. Full details of the inclusion and exclusion criteria for each study have been published previously (20, 24).

In each study, patients reported whether they had been previously treated with omalizumab, duration of treatment, and the reason for discontinuation. Patients were only eligible for inclusion into either study if they had not received omalizumab for ≥130 days before study start and patients were not permitted to start omalizumab treatment during the study.

Both study protocols were approved by local or national ethics committees. All patients provided written informed consent.

Study assessments

Spirometry and hematology measurements were collected at each clinic visit. The St George's Respiratory Questionnaire (SGRQ) was completed at randomization and study end. Patients recorded morning peak expiratory flow (PEF) daily using an electronic diary (eDiary, PHT). In MENSA, the Asthma Control Questionnaire (ACQ-5) was completed at each clinic visit, whereas in SIRIUS ACQ-5 scores were collected weekly and monitored closely throughout the study using the electronic diary. Safety was evaluated by the assessment of adverse events (AEs), laboratory data, vital signs, electrocardiograms, and immunogenicity.

Exacerbations were defined as worsening of asthma requiring the use of systemic corticosteroids for ≥3 days and/or

hospitalization and/or emergency department visit. For patients on maintenance OCS, at least double the maintenance dose was required for ≥3 days to meet the definition of an exacerbation.

Outcomes and statistical analyses

The primary outcome in MENSA was the annual rate of exacerbations. Other outcomes included forced expiratory volume in 1 s (FEV_1), morning PEF, ACQ-5 and SGRQ scores, blood eosinophil count, total IgE, and safety. In SIRIUS, the primary outcome was the percentage reduction in OCS dose. Secondary outcomes included the proportion of patients with a ≥50% reduction in OCS dose; the number of patients who achieved a total reduction in OCS dose; the median percentage reduction from baseline in daily OCS; the annual rate of exacerbations; FEV_1; morning PEF; ACQ-5 and SGRQ scores; blood eosinophil count; total IgE; and safety.

Post hoc analyses were performed on the intent-to-treat (ITT) population (all patients who underwent randomization and received at least one dose of study drug) from each study. Patients who had previously been treated with omalizumab were identified in each study, and separate models were used to evaluate each subgroup: patients with and without prior omalizumab treatment.

In the MENSA study, responses in the two mepolizumab treatment groups (75 mg IV and 100 mg SC) were broadly similar (24); therefore, these treatment groups were pooled in these *post hoc* analyses. Rate of exacerbations was estimated using negative binomial models (28). Each model included covariates for treatment, the use of maintenance OCS, geographic region, the number of exacerbations in the previous year, and baseline percentage of the predicted FEV_1. Mixed-model, repeated-measures methods were used to analyze data regarding questionnaire responses (ACQ-5 and SGRQ), lung function (FEV_1 and morning PEF), blood eosinophil counts, and IgE data. Models included the aforementioned covariates, plus baseline value, visit, and terms for the interaction of visit with baseline value and visit with treatment group.

In the SIRIUS study, the primary outcome categories of percentage reduction in OCS dose were analyzed using proportional odds models. Each model included covariates for treatment, geographic region, duration of OCS use (<5 years *vs* ≥5 years), and baseline OCS dose. Binary logistic regression models with adjustment for covariates were used to analyze the percentage of patients with specific reductions in OCS dose. The median percentage reduction in OCS dose was estimated using the Hodges–Lehmann estimation. Changes from baseline to week 24 in ACQ-5 and SGRQ scores, FEV_1, PEF, blood eosinophil count, and IgE data were analyzed using a mixed-model, repeated-measures approach after adjustment for covariates.

For both studies, a prespecified log transformation was applied to blood eosinophil counts and IgE results before analysis. Statistical analyses were performed with SAS software (v 9.3; SAS Institute Inc., Cary, NC, USA) (29).

Results

Patients

A total of 711 eligible patients were evaluated: 576 from MENSA and 135 from SIRIUS. Baseline characteristics for each study are shown by prior omalizumab use in Table 1.

In MENSA, 75 patients (13%) had received omalizumab before the study for a median treatment duration of 12 months. Of the 74 patients who reported the frequency of their omalizumab use, 37 (50%) received it every 2 weeks. Of the 67 patients in whom omalizumab treatment failed, 50 (75%) discontinued due to the lack of efficacy. Other reasons for discontinuation were cost (10%), side-effects (6%), inconvenient to visit the clinic (1%), and other (7%). Compared with patients without prior omalizumab treatment, patients previously treated with omalizumab had a longer duration of asthma, greater OCS maintenance use, lower FEV_1, worse ACQ-5 and SGRQ scores, higher IgE and eosinophil levels, and a higher incidence of hospitalizations or emergency department visits in the previous year, indicating that they had more severe disease (Table 1). The most commonly self-reported causes of previous exacerbations in patients with and without prior omalizumab use were cold air/cold weather (49% *vs* 52%), upper respiratory tract infection (other than the common cold; 56% *vs* 51%), and common cold (63% *vs* 46%).

In SIRIUS, 45 patients (33%) had previously used omalizumab for a median duration of 8 months; 37 (82%) discontinued omalizumab therapy due to the lack of efficacy. Other reasons for discontinuation were side-effects (9%), inconvenient to visit the clinic and cost (both 4%). In patients previously treated with omalizumab, baseline OCS dose, total IgE, and eosinophil levels were higher, and FEV_1 appeared lower than in patients without prior omalizumab; however, prior exacerbation frequency was similar across the two subgroups (Table 1). Among patients without prior omalizumab treatment, the most commonly reported causes of previous exacerbations were lower (58%) or upper (56%) respiratory tract infection, followed by common cold (40%). In the group that was previously treated with omalizumab, the most common causes of previous exacerbations were cold air/cold weather (67%), allergy (58%), and tobacco smoke (51%).

Efficacy of mepolizumab

In MENSA, mepolizumab reduced the rate of exacerbations by 57%, relative to placebo, in patients with prior omalizumab treatment. This reduction was comparable to that observed in patients who had not received prior omalizumab treatment (47%) (Fig. 1A and Table 2). In SIRIUS, patients previously treated with omalizumab had a similar OCS reduction following mepolizumab, compared with patients having no prior omalizumab history (Table 3). The proportion of patients with no decrease in OCS use, lack of asthma control, or early withdrawal was higher in the group that had previously received omalizumab than in the group that had not. However, the proportion of patients within this

Table 1 Baseline characteristics by prior omalizumab use (intent-to-treat population)

	MENSA				SIRIUS					
	Prior OMA use		No prior OMA use		Prior OMA use		No prior OMA use		Total	
Characteristics	PBO (*N* = 21)	MEPO (*N* = 54)	PBO (*N* = 170)	MEPO (*N* = 331)	PBO (*N* = 22)	MEPO (*N* = 23)	PBO (*N* = 44)	MEPO (*N* = 46)	Prior OMA use (*N* = 120)	No prior OMA use (*N* = 591)
Age, mean (range) years	48.0 (22–75)	50.0 (13–76)	49.3 (12–76)	50.7 (12–82)	47.8 (31–64)	44.3 (16–70)	51.0 (28–70)	52.6 (23–74)	48.2 (13–76)	50.5 (12–82)
Female, *n* (%)	10 (48)	34 (63)	97 (57)	188 (57)	8 (36)	13 (57)	22 (50)	31 (67)	65 (54)	338 (57)
Race, *n* (%)										
Caucasian	17 (81)	42 (78)	131 (77)	261 (79)	22 (100)	22 (96)	39 (89)	45 (98)	103 (86)	476 (81)
Black	0	6 (11)	3 (2)	7 (2)	0	0	0	0	6 (5)	10 (2)
Asian	4 (19)	6 (11)	34 (20)	61 (18)	0	1 (4)	2 (5)	0	11 (9)	97 (16)
Other	0	0	2 (1)	2 (<1)	0	0	3 (7)	1 (2)	0	8 (1)
Hispanic ethnicity, *n* (%)	1 (5)	3 (6)	14 (8)	33 (10)	0	0	3 (7)	2 (4)	4 (3)	52 (9)
BMI, mean (SD) kg/m^2	28.6 (7.96)	28.9 (6.33)	28.0 (5.25)	27.4 (5.87)	28.8 (6.78)	27.6 (4.92)	29.9 (5.70)	28.0 (6.37)	28.6 (6.43)	27.8 (5.75)
Former smoker, *n* (%)	2 (10)	13 (24)	55 (32)	89 (27)	7 (32)	7 (30)	18 (41)	21 (46)	29 (24)	183 (31)
Duration of asthma, mean (SD) years	23.6 (16.27)	21.4 (13.18)	19.1 (14.37)	19.9 (13.50)	18.2 (12.99)	13.8 (8.80)	21.0 (15.07)	19.3 (12.72)	19.7 (13.31)	19.7 (13.79)
Daily OCS use, *n* (%)	7 (33)	32 (59)	36 (21)	64 (19)	22 (100)	23 (100)	44 (100)	46 (100)	84 (70)	190 (32)
OCS dose*, mean (SD) mg/day	12.1 (7.56)	14.6 (9.37)	15.7 (15.96)	11.2 (10.52)	14.9 (6.57)	13.6 (8.88)	12.4 (6.00)	11.7 (6.17)	14.2 (8.33)	12.4 (10.19)
Eosinophils (cells/μl) inclusion criteria, *n* (%)										
≥300 in previous 12 months	15 (71)	37 (69)	106 (62)	239 (72)	17 (77)	19 (83)	25 (57)	31 (67)	88 (73)	401 (68)
≥150 at screening	21 (100)	42 (78)	146 (86)	268 (81)	20 (91)	21 (91)	40 (91)	40 (87)	104 (87)	494 (84)
% predicted pre-BD FEV_1, mean (SD)	53.9 (14.16)	57.2 (16.93)	63.5 (18.26)	60.8 (18.05)	52.2 (22.07)	56.6 (18.04)	60.6 (16.05)	61.1 (16.51)	55.6 (17.65)	61.6 (17.85)
Pre-BD FEV_1/FVC, mean (SD)	0.59 (0.10)	0.63 (0.12)	0.65 (0.13)	0.64 (0.13)	0.58 (0.13)	0.61 (0.12)	0.62 (0.11)	0.65 (0.13)	0.61 (0.12)	0.64 (0.13)
% reversibility FEV_1 at screening, mean (SD)	25.6 (23.26)	30.5 (31.21)	27.4 (19.97)	27.5 (22.34)	25.2 (18.21)	23.9 (13.71)	23.0 (18.94)	25.4 (21.73)	27.4 (25.04)	27.0 (21.37)
Morning PEF, mean (SD) l/min	266.0 (122.16)	251.1 (104.49)	278.3 (103.71)	263.6 (110.70)	313.6 (171.23)	277.8 (122.12)	311.0 (144.02)	288.2 (127.26)	270.3 (125.85)	273.3 (113.42)
ACQ-5 score, mean (SD)	3.09 (1.31)	2.47 (1.29)	2.18 (1.14)	2.14 (1.19)	2.11 (1.25)	2.17 (1.43)	1.93 (1.15)	2.14 (1.20)	2.45 (1.34)	2.14 (1.17)
SGRQ score, mean (SD)	60.9 (17.30)	51.5 (19.51)	45.2 (19.43)	45.3 (19.38)	47.9 (19.11)	52.5 (18.21)	43.6 (18.06)	48.2 (17.64)	52.7 (19.03)	45.4 (19.15)
Total IgE, geometric mean (SD on $\log_e$ scale) U/ml	217.0 (1.21)	182.3 (1.37)	143.1 (1.55)	161.3 (1.51)	128.2 (0.90)	160.2 (1.13)	106.8 (1.50)	99.1 (1.29)	171.80 (1.22)	145.88 (1.51)
Blood eosinophil count, geometric mean (SD $\log_e$ scale) cells/μl	500 (0.80)	270 (1.06)	300 (0.94)	290 (1.01)	320 (1.02)	320 (1.33)	200 (0.96)	220 (1.19)	320 (1.08)	280 (1.01)

Table 1 (continued)

Characteristics	MENSA				SIRIUS				Total	
	Prior OMA use		No prior OMA use		Prior OMA use		No prior OMA use			
	PBO (*N* = 21)	MEPO (*N* = 54)	PBO (*N* = 170)	MEPO (*N* = 331)	PBO (*N* = 22)	MEPO (*N* = 23)	PBO (*N* = 44)	MEPO (*N* = 46)	Prior OMA use (*N* = 120)	No prior OMA use (*N* = 591)
Severe exacerbations in previous year, mean (SD)	3.8 (2.30)	3.9 (2.31)	3.5 (2.81)	3.6 (2.52)	2.7 (2.47)	3.7 (4.07)	3.0 (2.91)	3.2 (3.04)	3.6 (2.76)	3.5 (2.68)
Exacerbations in previous year requiring hospitalization and/or ED visit, *n* (%)										
≥1	11 (52)	22 (41)	53 (31)	104 (31)	2 (9)	9 (39)	9 (20)	14 (30)	44 (37)	180 (30)
≥2	7 (33)	11 (20)	27 (16)	56 (17)	2 (9)	6 (26)	3 (7)	6 (13)	26 (22)	92 (16)
Exacerbations in previous year requiring hospitalization, *n* (%)										
≥1	9 (43)	14 (26)	26 (15)	60 (18)	1 (5)	5 (22)	8 (18)	9 (20)	29 (24)	103 (17)
≥2	5 (24)	7 (13)	12 (7)	22 (7)	0	2 (9)	3 (7)	5 (11)	14 (12)	42 (7)

ACQ, Asthma Control Questionnaire; BD, bronchodilator; BMI, body mass index; ED, emergency department; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IgE, immunoglobulin E; ITT, intent-to-treat; MEPO, mepolizumab; OCS, oral corticosteroid; OMA, omalizumab; PBO, placebo; PEF, peak expiratory flow; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

*Mean (SD) is only for those patients using daily OCS (patients not taking daily OCS were not included).

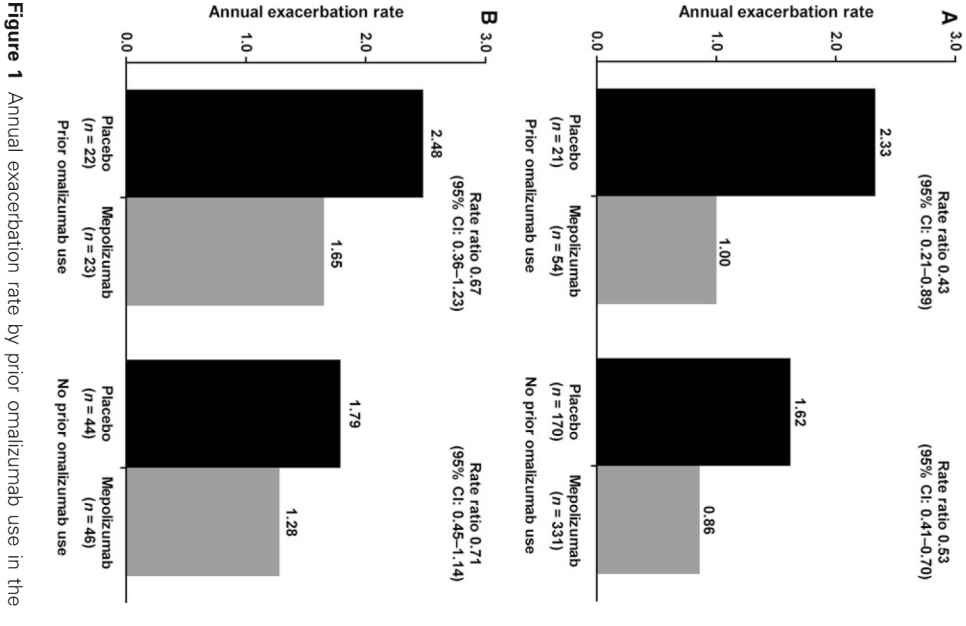

Figure 1 Annual exacerbation rate by prior omalizumab use in the (A) MENSA and (B) SIRIUS studies (intent-to-treat population).

lowest category was greater for placebo than for mepolizumab treatment, in both subgroups.

In addition to reducing OCS use, mepolizumab resulted in comparable reductions in the exacerbation rate, relative to placebo, regardless of prior history of omalizumab treatment (Fig. 1B and Table 3).

ACQ-5 and SGRQ scores were reduced with mepolizumab treatment compared with placebo, in both studies and in each of the subgroups investigated, indicating an improvement in asthma control and quality of life (Tables 2 and 3).

Mepolizumab-treated patients experienced significant decreases in blood eosinophil levels compared with those who received placebo, independent of prior omalizumab treatment (Tables 2 and 3). No significant change in IgE levels was observed in either study or subgroup analyzed (Tables 2 and 3).

A greater improvement in lung function, measured by FEV_1 and morning PEF, with mepolizumab was noted in MENSA for those patients without prior omalizumab treatment compared with patients who were previously treated with omalizumab (Table 2). In SIRIUS, an improvement in FEV_1 and morning PEF was observed with mepolizumab treatment in both subgroups analyzed (Table 3).

Table 2 Efficacy parameters from MENSA by prior omalizumab use (intent-to-treat population)

	Prior OMA use		No prior OMA use	
Parameter	PBO ($N = 21$)	MEPO ($N = 54$)	PBO ($N = 170$)	MEPO ($N = 331$)
Annual exacerbation rate	2.33	1.00	1.62	0.86
Rate ratio MEPO/PBO (95% CI)	0.43 (0.21, 0.89)		0.53 (0.41, 0.70)	
Change from baseline in ACQ-5 score at week 32, mean (SE)	−0.29 (0.248)	−1.16 (0.147)	−0.52 (0.072)	−0.90 (0.052)
Difference MEPO-PBO (95% CI)	−0.87 (−1.46, −0.28)		−0.38 (−0.56, −0.21)	
Change from baseline in SGRQ score at week 32, mean (SE)	−8.9 (4.70)	−21.0 (2.84)	−8.8 (1.18)	−15.0 (0.84)
Difference MEPO-PBO (95% CI)	−12.1 (−23.5, −0.7)		−6.2 (−9.1, −3.3)	
Change from baseline in morning PEF during weeks 28–32, mean l/min (SE)	10 (19.1)	18 (11.2)	0 (4.7)	25 (3.4)
Difference MEPO-PBO (95% CI)	8 (−37, 53)		25 (13, 36)	
Change from baseline in pre-BD FEV_1 at week 32, mean ml (SE)	229 (102.9)	77 (62.3)	72 (33.0)	200 (23.7)
Difference MEPO-PBO (95% CI)	−152 (−396, 91)		128 (48, 208)	
Change from baseline in post-BD FEV_1 at week 32, mean ml (SE)	166 (125.9)	110 (73.5)	12 (35.9)	182 (25.4)
Difference MEPO-PBO (95% CI)	−57 (−359, 246)		170 (83, 257)	
Ratio to baseline in eosinophil count at week 32, geometric mean (SE on $\log_e$ scale) cells/μl	0.78 (0.215)	0.12 (0.130)	0.89 (0.072)	0.16 (0.051)
Ratio MEPO/PBO (95% CI)	0.16 (0.09, 0.26)		0.18 (0.15, 0.21)	
Ratio to baseline in total IgE at week 32, geometric mean (SE on $\log_e$ scale) U/ml	0.80 (0.135)	1.09 (0.080)	1.08 (0.040)	1.05 (0.028)
Ratio MEPO/PBO (95% CI)	1.36 (0.99, 1.87)		0.98 (0.89, 1.07)	

ACQ, Asthma Control Questionnaire; BD, bronchodilator; CI, confidence interval; FEV_1, forced expiratory volume in 1 s; IgE, immunoglobulin E; ITT, intent-to-treat; MEPO, mepolizumab; OMA, omalizumab; PBO, placebo; PEF, peak expiratory flow; SE, standard error; SGRQ, St George's Respiratory Questionnaire.

Safety and tolerability

In each study, the incidence of AEs and serious AEs was comparable between subgroups (Table 4). As previously published, only one death occurred in each study: due to a road traffic accident in MENSA (in the placebo group; without prior omalizumab treatment) and due to gastrointestinal hemorrhage and aspiration in SIRIUS (in the placebo group; with prior omalizumab treatment) (Table 4) (20, 24).

Discussion

Results from these *post hoc* analyses indicate that similar efficacy and safety findings were observed in both studies with or without prior omalizumab treatment. Mepolizumab treatment in patients who have severe eosinophilic asthma resulted in reductions in exacerbations, and improved asthma control and quality of life, irrespective of patients' history of omalizumab treatment. Patients previously treated with omalizumab also showed similar reductions in OCS use following mepolizumab, compared with patients with no prior history of omalizumab use.

In both studies, most patients in the prior omalizumab treatment subgroup reported that discontinuation was due to the lack of efficacy. Patients with a prior history of omalizumab treatment appeared to have clinical markers indicative of more severe disease than those with no prior omalizumab treatment. Therefore, the availability of an alternative treatment that targets eosinophilic inflammation is an important option for patients with severe disease that is unresponsive to an anti-IgE.

Additionally, within SIRIUS, cold air/weather and allergen exposure were the most common causes of previous exacerbations in patients with prior omalizumab use, while respiratory tract infections were the most common cause in patients without prior omalizumab treatment. However the causes of previous exacerbations followed a different pattern in

Table 3 Efficacy parameters from SIRIUS by prior omalizumab use (intent-to-treat population)

	Prior OMA use		No prior OMA use	
Parameter	PBO (*N* = 22)	MEPO (*N* = 23)	PBO (*N* = 44)	MEPO (*N* = 46)
OCS reduction from baseline category during weeks 20–24, *n* (%)				
90–100%	0	3 (13)	7 (16)	13 (28)
75–<90%	3 (14)	3 (13)	2 (5)	9 (20)
50–<75%	2 (9)	4 (17)	8 (18)	5 (11)
>0–<50%	3 (14)	2 (9)	4 (9)	5 (11)
No decrease, lack of asthma control, or early withdrawal	14 (64)	11 (48)	23 (52)	14 (30)
OR MEPO/PBO (95% CI)	2.15 (0.67, 6.90)		2.53 (1.15, 5.58)	
≥50% reduction from baseline in OCS dose during weeks 20–24	5 (23)	10 (43)	17 (39)	27 (59)
OR MEPO/PBO (95% CI)	2.53 (0.69, 9.32)		2.33 (0.93, 5.80)	
Total reduction from baseline in OCS dose, during weeks 20–24, *n* (%)	0	2 (9)	5 (11)	8 (17)
OR MEPO/PBO (95% CI)	NE		1.49 (0.39, 5.63)	
Median % reduction from baseline in daily OCS dose, during weeks 20–24	–12.5	33.3	0	66.7
Median difference (95% CI)	30.5 (–2.4, 100.0)		29.3 (0.0, 66.7)	
Annual exacerbation rate	2.48	1.65	1.79	1.28
Rate ratio MEPO/PBO (95% CI)	0.67 (0.36, 1.23)		0.71 (0.45, 1.14)	
Change from baseline in ACQ-5 score at week 24, mean (SE)	0.13 (0.222)	–0.30 (0.220)	–0.21 (0.155)	–0.76 (0.150)
Difference MEPO-PBO (95% CI)	–0.44 (–1.05, 0.18)		–0.55 (–0.98, –0.13)	
Change from baseline in SGRQ score at week 24, mean (SE)	–3.7 (2.99)	–7.1 (2.84)	–2.6 (2.05)	–9.8 (2.00)
Difference MEPO-PBO (95% CI)	–3.4 (–11.9, 5.0)		–7.2 (–12.9, –1.4)	
Change from baseline in morning PEF during weeks 20–24, mean (SE) l/min	9 (13.1)	23 (3.1)	3 (7.0)	17 (6.8)
Difference MEPO-PBO (95% CI)	14 (–24, 51)		13 (–6, 33)	
Change from baseline in pre-BD FEV_1 at week 24, mean (SE) ml	–10 (108.2)	182 (105.8)	–5 (64.2)	85 (62.5)
Difference MEPO-PBO (95% CI)	192 (–114, 499)		90 (–89, 268)	
Change from baseline in post-BD FEV_1 at week 24, mean (SE) ml	–22 (84.8)	236 (80.3)	–28 (57.6)	17 (57.6)
Difference MEPO-PBO (95% CI)	258 (16, 499)		45 (–118, 208)	
Ratio to baseline in eosinophil count at week 24, geometric mean (SE on $\log_e$ scale) cells/μl	1.17 (0.196)	0.15 (0.192)	1.44 (0.113)	0.26 (0.111)
Ratio MEPO/PBO (95% CI)	0.13 (0.08, 0.23)		0.18 (0.13, 0.24)	
Ratio to baseline in total IgE at week 24, geometric mean (SE on $\log_e$ scale) U/ml	1.14 (0.131)	1.08 (0.128)	1.27 (0.116)	1.12 (0.113)
Ratio MEPO/PBO (95% CI)	0.94 (0.65, 1.37)		0.88 (0.64, 1.22)	

ACQ, Asthma Control Questionnaire; BD, bronchodilator; CI, confidence interval; FEV_1, forced expiratory volume in 1 s; IgE, immunoglobulin E; ITT, intent-to-treat; MEPO, mepolizumab; NE, not estimable; OCS, oral corticosteroid; OMA, omalizumab; OR, odds ratio; PBO, placebo; PEF, peak expiratory flow; SE, standard error; SGRQ, St George's Respiratory Questionnaire.

Table 4 Summary of AEs from the MENSA and SIRIUS studies (intent-to-treat population)

Event, *n* (%)	MENSA				SIRIUS			
	Prior OMA use		No prior OMA use		Prior OMA use		No prior OMA use	
	PBO (*N* = 21)	MEPO (*N* = 54)	PBO (*N* = 170)	MEPO (*N* = 331)	PBO (*N* = 22)	MEPO (*N* = 23)	PBO (*N* = 44)	MEPO (*N* = 46)
Any AE	18 (86)	49 (91)	141 (83)	268 (81)	21 (95)	21 (91)	40 (91)	37 (80)
Related to study treatment	5 (24)	14 (26)	25 (15)	58 (18)	5 (23)	7 (30)	7 (16)	14 (30)
Leading to permanent discontinuation of study treatment/study withdrawal	2 (10)	0	2 (1)	1 (<1)	2 (9)	2 (9)	1 (2)	1 (2)
Any serious AE	5 (24)	6 (11)	23 (14)	24 (7)	4 (18)	0	8 (18)	1 (2)
Related to study treatment	0	0	1 (<1)	1 (<1)	0	0	0	0
Fatal AE	0	0	1 (<1)	0	1 (5)	0	0	0
Any on-treatment AE	18 (86)	49 (91)	140 (82)	264 (80)	21 (95)	20 (87)	40 (91)	37 (80)
Any on-treatment serious AE	5 (24)	6 (11)	22 (13)	24 (7)	4 (18)	0	8 (18)	1 (2)

AE, adverse event; ITT, intent-to-treat; MEPO, mepolizumab; OMA, omalizumab; PBO, placebo.

MENSA; cold air/weather, respiratory tract infections, and common cold were the most commonly reported, with no notable differences between the subgroups.

Eosinophilic inflammation and IgE production are promoted by Th2 cytokines, such as IL-5, IL-4, and IL-13. IL-4 and IL-13 are the major factors involved in Th2 differentiation and IgE class switching (30), whereas IL-5 is involved in eosinophil growth, survival, activation, and in mediating inflammation (31). IgE-mediated reactions are likely to be a major contributor to symptoms in allergic individuals. The role of allergy in activating Th2 is likely to explain the higher level of baseline eosinophils observed in patients in the prior omalizumab groups compared with the no prior omalizumab groups, for both MENSA and SIRIUS. As mepolizumab is a humanized monoclonal antibody against IL-5, it selectively inhibits eosinophilic airway inflammation. Therefore, a reduction in eosinophils after mepolizumab treatment is expected, as observed in the MENSA and SIRIUS studies.

Studies have reported that both mepolizumab and omalizumab significantly improved disease control, in terms of decreasing the rate of exacerbations, as add-on treatment to current asthma therapy (14, 15, 20, 22, 24, 32). Although most patients who are eligible for mepolizumab will not meet the criteria for receiving omalizumab, there is a subgroup of patients who are eligible for either mepolizumab or omalizumab treatment. In these analyses, we found that in the MENSA study the proportions of patients meeting the US and EU prescribing criteria for omalizumab were 30% (162/547) and 38% (209/547), respectively. In the SIRIUS study, 24% (30/126) and 30% (38/126) of patients met the US and EU prescribing criteria for omalizumab, respectively. The proportions in the MENSA study were comparable with those from DREAM (22), with 30% (185/614) and 38% (235/614) of patients meeting the US and EU prescribing criteria for omalizumab, respectively.

The conditions for stopping treatment with mepolizumab continue to be assessed; however, it is intended for long-term treatment. The need for continued therapy should be considered annually as a minimum, by physician assessment of the patient's disease severity and level of control of exacerbations. The challenge for the physician is to determine the appropriate treatment for the right patient.

Severe asthma is heterogeneous in nature, as supported by the results from cluster analyses (6, 33), and it is therefore of clinical relevance to identify biomarkers that predict response to therapy. The use of blood eosinophils as a biomarker to identify patients who are likely to respond to treatment in conjunction with clinical markers, such as history of exacerbations and/or dependency on daily OCS, offers an easy and practical way for identifying these patients.

Recent *post hoc* analysis with omalizumab reported that blood eosinophils, fractional exhaled nitric oxide (FeNO), and periostin are markers that identify a more pronounced response. The EXTRA study enrolled patients with uncontrolled severe persistent allergic asthma (34). After 48 weeks of omalizumab treatment, reductions in protocol-defined exacerbations were greater in high *vs* low subgroups for all three biomarkers: FeNO: 53% *vs* 16%;

eosinophils: 32% *vs* 9%; and periostin: 30% *vs* 3%, whereas a *post hoc* analysis demonstrated that neither total IgE level nor antigen-specific IgE has consistently been predictive of response to omalizumab (13, 35, 36). Our findings suggest that a lack of response to omalizumab initially does not preclude patients responding to subsequent mepolizumab treatment.

The current results should be considered in the context of the limitations of *post hoc* analyses. These *post hoc* findings were also not the primary objective of the original studies. It must be recognized therefore that the results should be considered as hypothesis generating. For example, the FEV_1 finding in the prior omalizumab treatment group of the MENSA study is an unexplained outlier within a consistent picture of positive benefits with mepolizumab in this patient population. The large placebo response observed in this group may provide some insight into this finding; however, various additional analyses did not offer any further understanding of this result. Nonetheless, the overall results are consistent with those from the original research, suggesting that they may be of clinical relevance, although further studies are needed to confirm the findings. Some of the data presented may be subject to recall bias as patients were asked about their past experience with omalizumab. Furthermore, there are currently no defined criteria for determining response to therapy in severe asthma, and while this would be helpful in clinical studies of mepolizumab, this also highlights the need to move toward goal-oriented therapy in daily practice.

Conclusion

This is the first report to describe the experience of using a biotherapy in a patient population whose asthma was unresponsive to a biologic treatment targeting the IgE pathway and who had then received an alternate treatment targeting the IL-5 pathway and eosinophilic inflammation. In summary, these *post hoc* analyses indicate that in the atopic phenotype of patients with severe eosinophilic asthma and a prior history of omalizumab use, mepolizumab was effective in reducing exacerbations and improving outcomes related to asthma control. Mepolizumab was also well tolerated. Thus, independent of prior omalizumab use, patients with severe eosinophilic asthma plus a history of exacerbations and/or dependency on daily OCS use (despite high-dose ICS plus at least one additional controller) are likely to benefit from treatment with mepolizumab.

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Conflicts of interest

AM has received personal fees and nonfinancial support from GSK, Novartis, Boehringer Ingelheim, AstraZeneca, Stallergènes, ALK, MundiPharma, and Meda Pharma. AB has received personal fees from GSK and Boehringer Ingelheim for advisory board participation, congress attendance, asthma and COPD clinical trial investigator; and nonfinancial support from Novartis and AstraZeneca for participation as an asthma and COPD clinical trial investigator. CMP, FCA, RGP, and SY are employed by GSK and hold GSK stocks/shares. HO was employed by GSK at the time of the analysis and initial manuscript development.

Author contributions

CMP, FA, SY, and HO assisted in the conception and design of the subgroup analyses. AM, AB, CMP, RGP, and HO contributed to the acquisition of data; CMP, FA, SY, RGP, and HO participated in data analysis and interpretation. All authors contributed to the review of the manuscript and provided final approval of the manuscript before submission.

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