



Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial

Geoffrey L Chupp, Eric S Bradford, Frank C Albers, Daniel J Bratton, Jie Wang-Jairaj, Linda M Nelsen, Jennifer L Trevor, Antoine Magnan, Anneke ten Brinke

Summary

Background Mepolizumab, an anti-interleukin-5 monoclonal antibody approved as add-on therapy to standard of care for patients with severe eosinophilic asthma, has been shown in previous studies to reduce exacerbations and dependency on oral corticosteroids compared with placebo. We aimed to further assess mepolizumab in patients with severe eosinophilic asthma by examining its effect on health-related quality of life (HRQOL).

Methods We did a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial (MUSCA) in 146 hospitals or research centres in 19 countries worldwide. Eligible participants were patients aged 12 years or older with severe eosinophilic asthma and a history of at least two exacerbations requiring treatment in the previous 12 months before screening despite regular use of high-dose inhaled corticosteroids plus other controller medicines. Exclusion criteria included current smokers or former smokers with a history of at least ten pack-years. We randomly assigned participants (1:1) by country to receive a subcutaneous injection of either mepolizumab 100 mg or placebo, plus standard of care, every 4 weeks for 24 weeks (the final dose was given at week 20). We did the randomisation using an interactive voice response system and a centralised, computer-generated, permuted-block design of block size six. The two treatments were identical in appearance and administered in a masked manner; patients, investigators, other site staff and the entire study team including those assessing outcomes data were also masked to group assignment. The primary endpoint was the mean change from baseline in the St George's Respiratory Questionnaire (SGRQ) total score at week 24 in the modified intention-to-treat (modified ITT) population (analysed according to their randomly assigned treatment). Safety was assessed in all patients who received at least one dose of trial medication (analysed according to the actual treatment received). This trial is registered with ClinicalTrials.gov, number NCT02281318.

Findings We recruited patients between Dec 11, 2014, and Nov 20, 2015, and the study was undertaken between Dec 11, 2014, and June 10, 2016. The modified ITT population comprised 274 patients assigned to mepolizumab 100 mg and 277 assigned to placebo. Mepolizumab versus placebo showed significant improvements at week 24 from baseline in SGRQ total score (least squares mean [SE] change from baseline -15.6 (1.0) vs -7.9 (1.0), a treatment difference of -7.7 (95% CI -10.5 to -4.9 ; $p < 0.0001$). No deaths occurred during the study. 192 (70%) of 273 patients who received mepolizumab and 207 (74%) of 278 who received placebo reported at least one on-treatment adverse event, the most common of which were headache (in 45 [16%] given mepolizumab vs 59 [21%] given placebo) and nasopharyngitis (in 31 [11%] given mepolizumab vs 46 [17%] given placebo). 15 (5%) and 22 (8%) patients had an on-treatment serious adverse event in the mepolizumab and placebo groups, respectively; the most common was asthma in both groups (in three [1%] given mepolizumab vs nine [3%] given placebo).

Interpretation Mepolizumab was associated with significant improvements in HRQOL in patients with severe eosinophilic asthma, and had a safety profile similar to that of placebo. These results add to and support the use of mepolizumab as a favourable add-on treatment option to standard of care in patients with severe eosinophilic asthma.

Funding GlaxoSmithKline.

Introduction

The long-term goals of asthma management are to achieve good symptom control, and to minimise any future risk of exacerbations, fixed airflow limitation, and side-effects of treatment.¹ Improving patients' health-related quality of life (HRQOL) is also important, and subjective data obtained from the patient's perspective can be useful for identifying changes in health status

and disease burden, allowing for treatment adjustments.² Improving HRQOL is of particular interest in severe eosinophilic asthma, which is characterised by recurrent exacerbations, poor disease control, accelerated lung function decline, and decreased HRQOL.³⁻⁵

HRQOL in patients with severe asthma can be assessed using the St George's Respiratory Questionnaire (SGRQ), a 50-item questionnaire developed for patients with

Lancet Respir Med 2017;
5: 390-400

Published Online

April 5, 2017

[http://dx.doi.org/10.1016/S2213-2600\(17\)30125-X](http://dx.doi.org/10.1016/S2213-2600(17)30125-X)

See [Comment](#) page 362

Yale Center for Asthma and Airway Disease, Yale School of Medicine, New Haven, CT, USA (Prof G L Chupp MD); Respiratory Therapeutic Area, GlaxoSmithKline (GSK), Research Triangle Park, NC, USA (E S Bradford MD); Respiratory Medical Franchise, GSK, Research Triangle Park, NC, USA (F C Albers MD); Clinical Statistics, GSK, Stockley Park, Middlesex, UK (D J Bratton PhD); Respiratory Therapy Area, GSK, Stockley Park, Middlesex, UK (J Wang-Jairaj MD); Value Evidence and Outcomes, GSK, Collegeville, PA, USA (L M Nelsen MHS); Division of Pulmonary, Allergy & Critical Care Medicine, University of Alabama at Birmingham, Birmingham, AL, USA (J L Trevor MD); l'Institut du Thorax, Université de Nantes, CHU de Nantes, Nantes, France (Prof A Magnan MD); and Department of Respiratory Medicine, Medical Centre Leeuwarden, Leeuwarden, Netherlands (A ten Brinke MD)

Correspondence to:

Prof Geoffrey L Chupp, Yale Center for Asthma & Airway Diseases, New Haven, CT 06520-8057, USA
geoffrey.chupp@yale.edu

Research in context

Evidence before this study

The anti-interleukin-5 monoclonal antibody mepolizumab is approved as an add-on therapy in Europe, Canada, USA, and other countries, to standard of care for the treatment of patients with severe eosinophilic asthma. Mepolizumab has been shown to reduce exacerbation rates and dependency on oral corticosteroid use in clinical trials in patients with severe eosinophilic asthma. However, less evidence is available for its effect on health-related quality of life (HRQOL), a particularly important consideration for patients with severe eosinophilic asthma, which is characterised by recurrent exacerbations, poor disease control, accelerated lung function decline, and worse HRQOL compared with milder forms of asthma. Much of the available evidence comes from the assessment of responses to the Asthma Control Questionnaire (ACQ)-5, a targeted questionnaire focused on specific symptoms (night-time waking, activity limitation, shortness of breath or wheezing, and rescue medication use for assessing asthma control). The St George's Respiratory Questionnaire (SGRQ) is an alternative assessment of respiratory health status that evaluates a range of respiratory experiences including symptoms, physical activity, and effect on HRQOL, providing a wider perspective on treatment effect in patients with severe disease. We searched PubMed for English-language studies of mepolizumab on HRQOL published up to Dec 13, 2016, using the search terms "mepolizumab", "eosinophilic asthma", and "quality of life OR asthma control questionnaire OR St George's Respiratory Questionnaire". The search identified seven publications presenting data from four clinical trials, ranging in duration from 11 to 52 weeks. In three of the four trials (Halder

and colleagues, SIRIUS, and MENSA), significant improvements occurred in HRQOL with mepolizumab compared with placebo, as assessed with the SGRQ, ACQ-5, or Asthma Quality of Life Questionnaire. However, HRQOL was assessed as a secondary endpoint in all four trials, and where the SGRQ was used, scores were generally assessed only at baseline and at the study end, resulting in too few data to fully assess the effect of mepolizumab on HRQOL over time.

Added value of this study

To our knowledge, this study was the first clinical trial designed primarily to assess the effect of mepolizumab on disease-specific HRQOL using the SGRQ in patients with severe eosinophilic asthma. We showed that early and sustained improvements occurred in disease-specific HRQOL with mepolizumab compared with placebo in patients with severe eosinophilic asthma. Our findings provide valuable new evidence to help to understand the effect of mepolizumab on the daily lives of patients in this population.

Implications of all the available evidence

Our results are consistent with, and build upon, those from previous studies. Evidence to date suggests that mepolizumab treatment decreases exacerbation rates, reduces oral corticosteroid use, and improves HRQOL in patients with severe eosinophilic asthma. Given that achieving good symptom control, minimising future risk of exacerbations, and improving HRQOL are key goals in asthma management, mepolizumab provides a favourable add-on treatment option to standard of care for patients with severe eosinophilic asthma.

chronic airflow limitation.^{6,7} The SGRQ assesses symptoms, physical activity, and the effect of the disease on the patient's life, and can therefore provide a wider perspective on treatment effectiveness in patients with severe asthma compared with more targeted questionnaires such as the Asthma Control Questionnaire (ACQ)-5.⁸ The SGRQ is scored from 0–100, with higher scores indicating worse HRQOL; a four-point reduction in score is considered to be the minimal clinically important difference (MCID), defined as the individual patient score change over a predetermined period that should be interpreted as a treatment benefit.^{9–11} Findings from a previous study¹² have confirmed the content validity of the SGRQ in patients with severe asthma. HRQOL data in patients with asthma can be further supplemented by the assessment of other indicators of asthma impact on patients, and control including lung function and ACQ-5 scores, providing a fuller perspective on the overall treatment benefits.

Mepolizumab is an anti-interleukin-5 monoclonal antibody that is approved in Europe, Canada, USA, and other countries as an add-on therapy to standard of care for the treatment of patients with severe eosinophilic

asthma.^{13,14} Results from previous studies showed significant reductions in exacerbation rates^{15,16} and dependency on oral corticosteroid use¹⁷ with mepolizumab treatment compared with placebo in patients with severe eosinophilic asthma, both in addition to standard of care. In these trials, treatment with mepolizumab resulted in significant improvements in SGRQ and ACQ-5 scores compared with placebo; however, SGRQ was only assessed as a secondary endpoint with collection of data at baseline and the end of treatment,^{16,17} resulting in too few data to fully assess the effect of mepolizumab on HRQOL. Additionally, although improvements in lung function have been shown with mepolizumab treatment, the degree of improvement varied between studies.^{15,16} Further investigation of the efficacy of mepolizumab on lung function in asthma was therefore warranted. We undertook the MUSCA clinical trial, designed mainly to assess the effect of mepolizumab on disease-specific HRQOL—using the SGRQ—in patients with severe eosinophilic asthma. We also examined the effects of mepolizumab on lung function and asthma symptom control as secondary objectives, providing a broader view of potential treatment benefits.

Methods

Study design and participants

See Online for appendix

We did a phase 3b, placebo-controlled, double-blind, parallel-group, multicentre study in 146 hospitals or research centres in 19 countries (Argentina, Belgium, Bulgaria, Canada, Czech Republic, Estonia, France, Germany, Greece, Italy, Netherlands, Norway, Peru, Russia, Slovakia, Spain, Ukraine, UK, and USA). We did the study in accordance with the applicable country-specific regulatory ethics requirements in individual countries. The protocol for this study is available online from the GSK Clinical Study Register (number 200862).¹⁸

For the **protocol** see <https://www.gsk-clinicalstudyregister.com/>

We enrolled patients aged 12 years or older with severe eosinophilic asthma who had experienced at least two exacerbations requiring treatment with systemic corticosteroids in the previous 12 months (for patients on maintenance oral corticosteroids, two-fold or greater dose increases were required for inclusion), despite treatment with regular high-dose inhaled corticosteroids in the 12 months before screening, plus additional controller medication(s) for at least 3 months before screening. Participants were also required to have airflow obstruction as indicated by a pre-bronchodilator FEV₁ of less than 80% predicted in those aged ≥18 years, or less than 90% predicted in those aged 12–17 years, as per the criteria for severe uncontrolled asthma of the European Respiratory Society/American Thoracic Society joint guidelines.⁴

Current or former smokers with a smoking history of ten pack-years or more were excluded, as were individuals with a concurrent respiratory disease and those who had received omalizumab within 130 days before screening. Patients were also excluded if they had severe or clinically significant cardiovascular disease, or other eosinophilic diseases. After a 1–4-week run-in period after the screening visit, patients eligible to be randomly assigned to treatment had to demonstrate an eosinophilic phenotype, characterised by a blood eosinophil count of at least 300 cells per μ L within the 12 months before screening, or a blood eosinophil count of at least 150 cells per μ L at screening (these thresholds were established from the analysis of the DREAM study, in which they best predicted patients who were likely to respond to mepolizumab). All patients, and their parent or guardian

if they were younger than 18 years, provided written informed consent. Additional inclusion, exclusion, and randomisation criteria are in the appendix.

Randomisation and masking

We randomly assigned patients (1:1) to receive a subcutaneous injection of either mepolizumab 100 mg (GSK, GSK Manufacturing Strada Provinciale Parma, Italy) or placebo using an interactive voice response system. The randomisation sequence was centrally computer generated using a permuted-block design of block size six, and the randomisation was done separately for each country. At each study centre, formulations of mepolizumab and placebo were prepared by staff members who were aware of study-group assignments but were not involved in study assessments. The two preparations were identical in appearance and were administered in a masked manner. Patients, investigators, other site staff, and the entire study team including those assessing outcomes data were masked to treatment assignment.

Procedures

Patients who successfully completed the run-in period received either mepolizumab or placebo every 4 weeks for 24 weeks in addition to standard of care (figure 1). The last dose was given at week 20. Spirometry measurements were taken at screening, baseline, and every 4 weeks until week 24. SGRQ total and domain scores were recorded at baseline, and at weeks 4, 12, 20, and 24 (SGRQ was not recorded at weeks 8 and 16 to reduce the burden on patients). ACQ-5 scores were recorded and exacerbation reviews were undertaken at baseline and every 4 weeks until week 24.

Outcomes

The primary efficacy endpoint was the mean change from baseline in SGRQ total score at week 24. SGRQ domain scores (symptoms, activity, and impact) were assessed as other endpoints. Secondary endpoints (all measured at week 24) were the mean change from baseline in pre-bronchodilator FEV₁, the proportion of SGRQ total score responders (ie, patients achieving a ≥four-point reduction from baseline in SGRQ score), and the mean change from baseline in ACQ-5 score. Other patient-reported outcome endpoints assessed at week 24 were the proportion of ACQ-5 responders (ie, patients achieving a ≥0·5-point reduction from baseline in ACQ-5 score), daily asthma symptom scores (measured on six-point scale [appendix]), bronchodilator use, and morning peak expiratory flow (PEF) as assessed by electronic diary. Other lung function parameters assessed at week 24 were the mean change from baseline in post-bronchodilator FEV₁, pre-bronchodilator or post-bronchodilator forced vital capacity (FVC), and pre-bronchodilator forced expiratory flow (FEF)_{25–75} (ie, FEF at 25–75% of FVC).

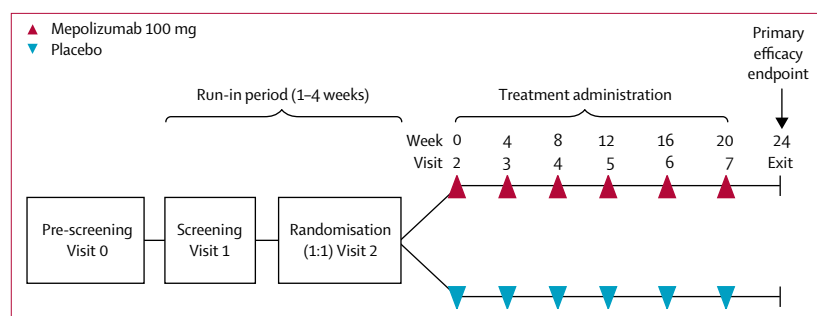


Figure 1: Trial design

Other endpoints included the annual rate of clinically significant exacerbations (defined as worsening of asthma requiring systemic corticosteroids administered intravenously or orally for ≥ 3 days or as a single intramuscular dose, or an emergency room visit or admission to hospital), exacerbations requiring an emergency room visit or admission to hospital, and exacerbations requiring admission to hospital.

Safety assessments included reported adverse events and serious adverse events, including systemic and injection site reactions, clinically significant changes in haematological variables (assessed at baseline and weeks 12 and 24) or clinical chemistry variables (assessed at baseline, and weeks 4, 8, 12, and 24); 12-lead electrocardiograms, assessed at baseline and weeks 12 and 24; and immunogenicity, assessed using an anti-mepolizumab bridging immunoassay (an indirect ligand-binding immunoassay that uses electrochemiluminescent detection) at baseline and week 24. We also undertook physical examinations at baseline and week 24 and measured vital signs every 4 weeks until week 24.

Statistical analysis

We estimated that, with a sample size of 544 patients (272 per group), the study had a 98% probability of achieving a statistically significant between-group difference for SGRQ total score, assuming a true treatment difference of six points (SD 15.3). Additionally, this sample size had a 92% probability of achieving a difference of more than four points (MCID) between treatment groups.

All randomly assigned patients who received at least one dose of trial medication were included in the modified intention-to-treat (ITT) population for efficacy assessments, with patients analysed according to their randomised treatment. A per-protocol analysis, including all patients in the modified ITT population who were not identified as full protocol deviators, was also planned for supplementary analysis of the primary endpoint. Safety assessments were done in the safety population, which consisted of all randomly assigned patients who received at least one dose of trial medication, analysed according to the actual treatment received for more than half of the administrations. No interim data analyses were planned.

The study was designed to test the superiority of mepolizumab versus placebo. Significance tests were done at the two-sided 5% α level (one-sided 2.5%). To control the overall type I error rate for the primary and secondary endpoints, we used a hierarchical testing procedure whereby statistical significance of the primary endpoint led to testing of the secondary endpoints in a similar manner in the following pre-defined order: change from baseline in pre-bronchodilator FEV₁ at week 24; percentage of patients achieving at least a four-point reduction from baseline in SGRQ at week 24; and change from baseline in ACQ-5 score at week 24.

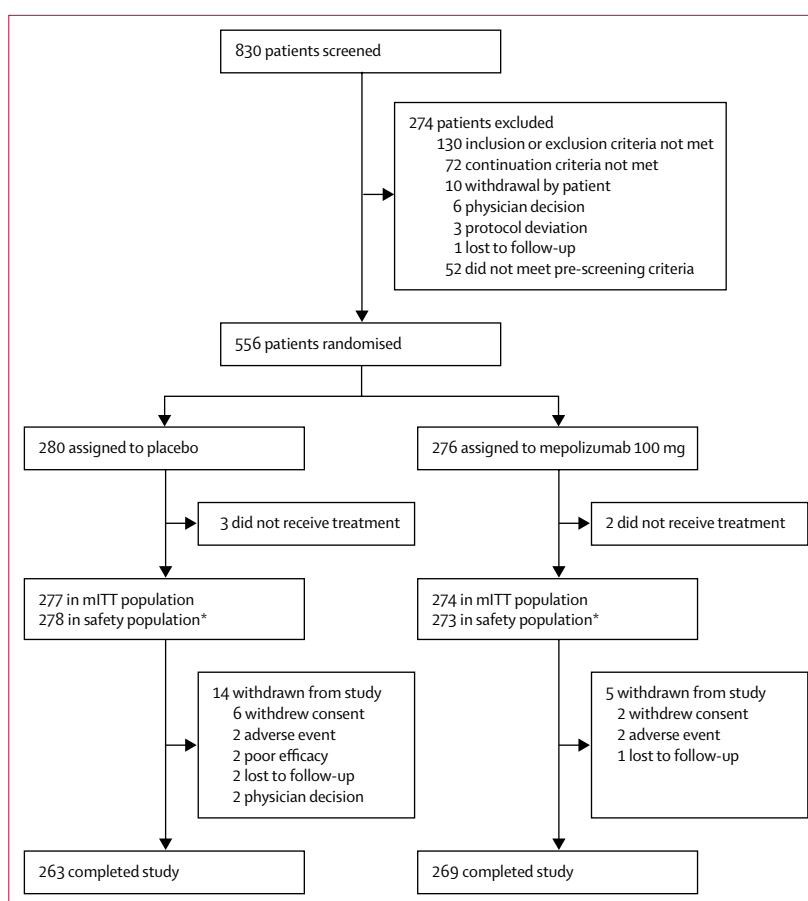


Figure 2: Trial profile

*One patient randomly assigned to mepolizumab received placebo in error and was therefore included in the placebo safety analysis (but was included in the mepolizumab modified intention-to-treat [ITT] efficacy analysis).

We investigated the effect of mepolizumab on SGRQ score, ACQ-5 score, pre-bronchodilator FEV₁, and the annual rate of exacerbations, according to baseline blood eosinophil count as a pre-specified analysis. We also did a non-predefined post-hoc analysis of the proportion of SGRQ and ACQ-5 responders by blood eosinophil count thresholds at baseline (≥ 150 , ≥ 300 , and ≥ 500 cells per μL).

For continuous endpoints, estimated absolute means, mean changes from baseline and estimated treatment differences (mepolizumab minus placebo) were calculated for each visit. Data were analysed using mixed-effect model repeat measures adjusting for baseline values, region, baseline maintenance oral corticosteroid therapy, exacerbations in the 12 months before the study, baseline percentage of predicted FEV₁ (excluding lung function endpoints), and interaction terms for visit by baseline and visit by treatment group as covariates. All data obtained up to and including week 24 were included in the model. Residuals were assessed to check model assumptions and no violations were noted.

Data for the percentage of patients achieving at least a four-point reduction in SGRQ at week 24 and the ACQ-5

response were analysed using a logistic regression model with baseline value, region, baseline maintenance oral corticosteroid therapy, exacerbations in the year before the study, and baseline percentage of predicted FEV₁ as covariates. Patients with a missing score at week 24 were included in the least favourable category in the analysis. Exacerbation rates were analysed using negative binomial regression with region, baseline maintenance oral corticosteroid therapy, exacerbations in the year before the study, and baseline percentage of predicted FEV₁ as covariates. Electronic diary endpoints were averaged over 4-week periods. We used univariate models to investigate the effect of baseline blood eosinophil count on the continuous primary and secondary outcomes at week 24 and clinically significant exacerbations, adjusting for the

same covariates as used in the main analysis of the corresponding endpoint and an interaction between treatment and log baseline blood eosinophil count. A data monitoring committee did not oversee the study. All analyses were done using SAS 9.3. This trial is registered with ClinicalTrials.gov, number NCT02281318.

Data sharing

Anonymised patient-level data underlying this study can be requested by qualified independent researchers, subject to review by an independent panel. To protect the privacy of patients and individuals involved in our studies, GSK does not publically disclose individual-level data.

Role of the funding source

The funder of study had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The funder did not place any restrictions on access to the data or statements made in the report. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

Results

We recruited patients between Dec 11, 2014, and Nov 20, 2015, and the study was undertaken between Dec 11, 2014, and June 10, 2016. Of 830 patients screened, 556 were randomly assigned to treatment. Five patients (three assigned to placebo and two assigned to mepolizumab) did not receive treatment as they were assigned in error, and one patient assigned to mepolizumab received placebo in error. Therefore, 551 patients were included in the modified ITT population (274 assigned to mepolizumab, 277 assigned to placebo), 273 were included in the mepolizumab safety population, and 278 in the placebo safety population (figure 2). Demographic and baseline disease characteristics were well balanced between the treatment groups, although there was a non-significantly higher proportion of female patients in the placebo group than in the mepolizumab group (table 1).

Mepolizumab treatment significantly improved SGRQ total score from baseline compared with placebo at week 24 (least squares mean [SE] change from baseline -15.6 [1.00] vs -7.9 [1.01], a treatment difference of -7.7 [95% CI -10.5 to -4.9 ; $p<0.0001$]. Improvements in SGRQ total score exceeded MCID from week 12 onwards for mepolizumab versus placebo (figure 3). Results of the per-protocol analysis of change in SGRQ total score from baseline with mepolizumab versus placebo were consistent with the modified ITT analysis (appendix). Treatment with mepolizumab also significantly improved SGRQ domain scores (symptoms, activity, and impact) from baseline at week 24 compared with placebo (table 2; figure 3). The number of SGRQ total score responders (≥ 4 -point improvement) at week 24 was greater in the mepolizumab group than in the placebo group (table 2).

For more on the research data see <https://protect-eu.mimecast.com/s/n1WrBTRJVLfo?domain=clinicalstudydatarequest.com>

	Placebo (n=277)	Mepolizumab 100 mg (n=274)
Age (years)	52.1 (12.9)	49.8 (14.0)
Sex		
Female	176 (64%)	149 (54%)
Male	101 (36%)	125 (46%)
Body-mass index (kg/m ²)	27.9 (6.2)	28.5 (6.6)
Former smoker	76 (27%)	71 (26%)
Duration of asthma (years)	19.6 (15.0)	19.5 (14.7)
Number of exacerbations in the 12 months before screening	2.7 (1.5)	2.9 (1.9)
Patients with ≥ 1 exacerbation requiring ER visit or admission to hospital in the 12 months before screening	92 (33%)	87 (32%)
Patients with ≥ 1 exacerbation requiring admission to hospital in the 12 months before screening	68 (25%)	69 (25%)
Current oral corticosteroid use	67 (24%)	64 (23%)
Oral corticosteroid dose (mg/day)	13.4 (10.8)	12.6 (11.0)
Current inhaled corticosteroid use	277 (100%)	273 (>99%)
Current LABA use	274 (99%)	273 (>99%)
Current LRA use	114 (41%)	108 (39%)
Current xanthine derivative use	56 (20%)	59 (22%)
Current LAMA use	63 (23%)	51 (19%)
Measures of lung function		
Pre-bronchodilator FEV ₁ (L)	1.7 (0.6)	1.8 (0.6)
Percentage of predicted pre-bronchodilator FEV ₁	55.2% (14.6)	55.5% (14.4)
Percentage of FEV ₁ reversibility	20.5% (21.6)	22.0% (23.2)
Pre-bronchodilator FVC (L)	2.9 (0.9)	3.1 (0.9)
Pre-bronchodilator FEF ₂₅₋₇₅ (mL/s)	869 (505)	919 (529)
Baseline blood eosinophil count		
Baseline geometric mean (10 ⁹ /L)	0.35	0.30
≥ 150 per μ L at screening	240 (87%)	234 (85%)
≥ 300 per μ L in 12 months before screening	165 (60%)	186 (68%)
Total SGRQ score	46.3 (18.9)	47.4 (18.1)
ACQ-5 score	2.2 (1.2)	2.2 (1.1)
Baseline presence of nasal polyps	47 (17%)	58 (21%)
Positive atopic status	124 (45%)	127 (46%)

Data are mean (SD) or n (%). ER=emergency room. LABA=long-acting β -2 agonist. LRA=leukotriene receptor antagonist. LAMA=long-acting muscarinic agonist. FVC=forced vital capacity. FEF₂₅₋₇₅=forced expiratory flow at 25–75% of FVC. SGRQ=St George's Respiratory Questionnaire. ACQ=Asthma Control Questionnaire.

Table 1: Baseline characteristics of the modified intention-to-treat population

The mean change from baseline in ACQ-5 score at week 24 was greater for patients treated with mepolizumab compared with placebo (table 2), and between-group differences in ACQ-5 change from baseline were evident from week 4 onwards (figure 4). Additionally, the proportion of patients who had a 0·5 point or more improvement (MCID) from baseline in ACQ-5 at week 24 was higher for mepolizumab than with placebo (table 2).

Mean changes from baseline in pre-bronchodilator FEV₁, FVC, and FEF₂₅₋₇₅ at week 24 were higher for patients treated with mepolizumab versus placebo (table 3). Pre-bronchodilator FEV₁ values improved early, and improvements were sustained up to week 24 (figure 4). Mean changes from baseline in post-bronchodilator FEV₁ and FVC were non-significantly higher at week 24 with mepolizumab versus placebo (data not shown). Improvements in daily asthma symptom scores and bronchodilator use at weeks 21–24 from baseline were similar between treatment groups (appendix), and mean changes from baseline in morning PEF in this period were non-significantly higher with mepolizumab compared with placebo (appendix).

The mean annualised rates of clinically significant exacerbations, and exacerbations requiring an emergency-room visit or admission to hospital, were significantly lower in the mepolizumab group versus the placebo group, resulting in yearly rate reductions of 58% and 68%, respectively. The annual rate of exacerbations requiring admission to hospital did not differ between groups (table 3).

192 (70%) of 273 patients who received mepolizumab and 207 (74%) of 278 patients who received placebo reported at least one on-treatment adverse event, and 31 (11%) and 25 (9%) patients reported at least one treatment-related adverse event in the mepolizumab and placebo groups, respectively (table 4). The most frequently reported adverse events in both the mepolizumab group and the placebo group were headache and nasopharyngitis. The occurrence of systemic and local injection site reactions was similar between groups (table 4). Two systemic reactions occurred in the mepolizumab group but neither was deemed a serious adverse event; two systemic reactions also occurred in the placebo group, both deemed as serious adverse events. 15 (5%) and 22 (8%) patients in the mepolizumab and placebo groups, respectively, had an on-treatment serious adverse event (in the placebo group, these included the two systemic reactions) during treatment. Of these, 12 were asthma-related: three (1%) in the mepolizumab group and nine (3%) in the placebo group. No patients died during the study. At the exit visits, (ie, at 24 weeks—4 weeks after the final dose) ten (4%) patients in the mepolizumab group and five (2%) patients in the placebo group tested positive for anti-mepolizumab antibodies with no evidence of neutralising anti-drug antibodies in either group. Clinical and laboratory parameters during the study were similar to baseline and between treatment groups (data not shown).

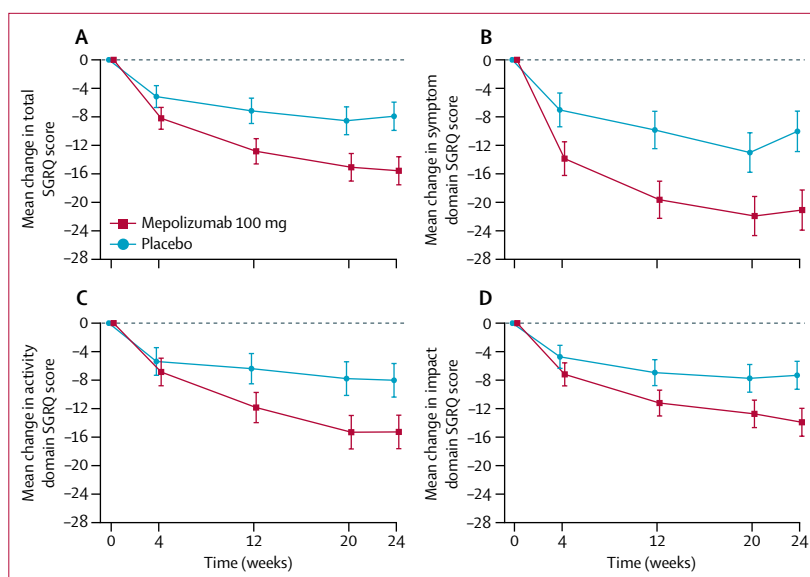


Figure 3: St George's Respiratory Questionnaire (SGRQ) scores at each visit

Figure shows adjusted mean changes (95% CI) from baseline in (A) total SGRQ score, (B) symptom domain SGRQ score, (C) activity domain SGRQ score, and (D) impacts domain SGRQ score.

Exploratory modelling of baseline blood eosinophil count indicated that mepolizumab treatment effects on the change from baseline in SGRQ total score were of similar magnitude across the range of baseline eosinophil counts (figure 5). However, predictive changes from baseline in ACQ-5 score, pre-bronchodilator FEV₁, and the annual rate of exacerbations suggested that mepolizumab treatment had a greater effect with higher baseline blood eosinophil counts, shown by diverging predicted values as baseline blood eosinophil count increased (figure 5).

A post-hoc analysis of the proportion of SGRQ and ACQ-5 responders by baseline blood eosinophil count showed that similar proportions of patients responded to mepolizumab across baseline eosinophil thresholds (≥ 150 , ≥ 300 , and ≥ 500 cells per μL ; appendix).

Discussion

In our study, mepolizumab treatment produced early and sustained improvements in HRQOL and markers of overall asthma control, including lung function and asthma symptoms, in patients with severe eosinophilic asthma. Additionally, mepolizumab treatment was associated with a reduction in exacerbations and had a safety profile consistent with placebo, as reported in previous studies.^{15–17}

Enrolled patients had similar demographic and baseline characteristics to those in previous mepolizumab clinical trials, with only minor differences in characteristics such as slightly higher baseline blood eosinophil counts and fewer exacerbations in the previous year compared with DREAM and MENSA.^{15,16} By contrast with previous studies, MUSCA assessed the effect of mepolizumab on HRQOL throughout the study and showed substantial

	Placebo (n=277)	Mepolizumab 100 mg (n=274)	Treatment difference (95% CI; p value)
SGRQ total score at week 24 (primary endpoint)			
Baseline SGRQ total score	46.3 (18.9)	47.4 (18.1)	..
Change from baseline	-7.9 (1.0) [n=260]	-15.6 (1.0) [n=265]	..
SGRQ domain scores at week 24			
Symptom domain			-11.0 (-15.1 to -7.0; p<0.0001)
Baseline symptom domain score	57.6 (24.3)	59.9 (22.7)	..
Change from baseline	-10.0 (1.5) [n=261]	-21.1 (1.4) [n=266]	..
Activity domain			-7.2 (-10.6 to -3.9; p<0.0001)
Baseline activity domain score	56.1 (22.0)	57.2 (20.5)	..
Change from baseline	-8.0 (1.2) [n=261]	-15.3 (1.2) [n=265]	..
Impacts domain			-6.6 (-9.4 to -3.8; p<0.0001)
Baseline impacts domain score	37.1 (20.3)	38.0 (20.4)	..
Change from baseline	-7.3 (1.0) [n=262]	-13.9 (1.0) [n=266]	..
SGRQ responders*			2.2 (1.6 to 3.2; p<0.0001)
SGRQ responders at week 24	151 (55%) [n=275]	198 (73%) [n=273]	..
ACQ-5 score at week 24			-0.4 (-0.6 to -0.2; p<0.0001)
Baseline ACQ-5 score	2.2 (1.2)	2.2 (1.1)	..
Change from baseline	-0.4 (0.1) [n=261]	-0.8 (0.1) [n=266]	..
ACQ-5 responders			2.0 (1.4 to 2.8; p=0.0014)
ACQ-5 responders† at week 24	116 (42%) [n=276]	161 (59%) [n=274]	..

Data are mean (SD) for baseline scores, least-squares mean (SE) for changes from baseline, or n (%), except where otherwise stated. Treatment differences for responder analyses are presented as odds ratios. *SGRQ total score responders defined as patients achieving a reduction of four points or more from baseline in SGRQ score at week 24. †ACQ-5 score responders defined as patients achieving a reduction of 0.5 points or more from baseline in ACQ-5 score at week 24.

Table 2: St George's Respiratory Questionnaire (SGRQ) and Asthma Control Questionnaire (ACQ)-5 endpoints in the modified intention-to-treat population

improvements in SGRQ scores with mepolizumab compared with placebo by week 12; these improvements were approximately twice the MCID¹⁰ by week 24. This early and sustained response in SGRQ score has not been investigated in previous mepolizumab studies.^{16,17} The change in SGRQ total score from baseline with mepolizumab treatment versus placebo in this study compares favourably with the approximate changes of 1.5–4.0 units reported with long-acting bronchodilator therapies such as salmeterol and formoterol, and the 4–5 unit changes reported with long-acting bronchodilator combination therapies in patients with COPD.^{19–21} Furthermore, patients receiving mepolizumab were more likely to have a clinically significant four-point improvement in total SGRQ score versus placebo after 4 weeks of treatment, which was sustained through to week 24. The symptoms domain for the mepolizumab group had the earliest clear separation from placebo compared with the other domain scores, which suggests that the early improvements in the total score were driven mainly by the symptoms domain and the early and sustained improvements in lung function. Changes in the activity and impacts domains with mepolizumab and placebo were clearly separated by week 12 and week 4, respectively, (impact domain mean treatment difference at week 4 was -2.5, 95% CI -4.7 to -0.2; p=0.035), and these differences were sustained to week 24. These results support the responsiveness of the SGRQ in patients with

severe eosinophilic asthma, and provide more comprehensive treatment response data than those previously provided in the MENSA study,¹⁶ which only assessed SGRQ scores at the beginning and end of the study (SGRQ was not assessed in DREAM).

Mepolizumab treatment produced significant improvements in ACQ-5 scores from week 4 onwards, which were maintained through to week 24. Additionally, the proportion of patients with an improvement of at least 0.5 points (MCID)²² from baseline in ACQ-5 at week 24 was higher for mepolizumab compared with placebo. However, the difference in mean change from baseline in ACQ-5 scores between the mepolizumab group and the placebo group was less than the MCID (0.5 units) at all timepoints; this finding contrasts with the improvements in SGRQ score, which exceeded the MCID by week 12. In the MENSA study, greater improvements in ACQ-5 scores occurred with mepolizumab treatment compared with placebo from week 4 through to week 32.¹⁶

Differences in the ability of SGRQ and ACQ-5 to detect clinically significant improvements in HRQOL and asthma control, respectively, might be attributable to several factors. Patients with eosinophilic inflammation have more poorly controlled asthma and higher exacerbation rates than individuals with less severe disease.^{4,23} In patients with eosinophilic inflammation, small airway inflammation might lead to dynamic hyperinflation, an effect that occurs in patients with eosinophilic asthma.²⁴

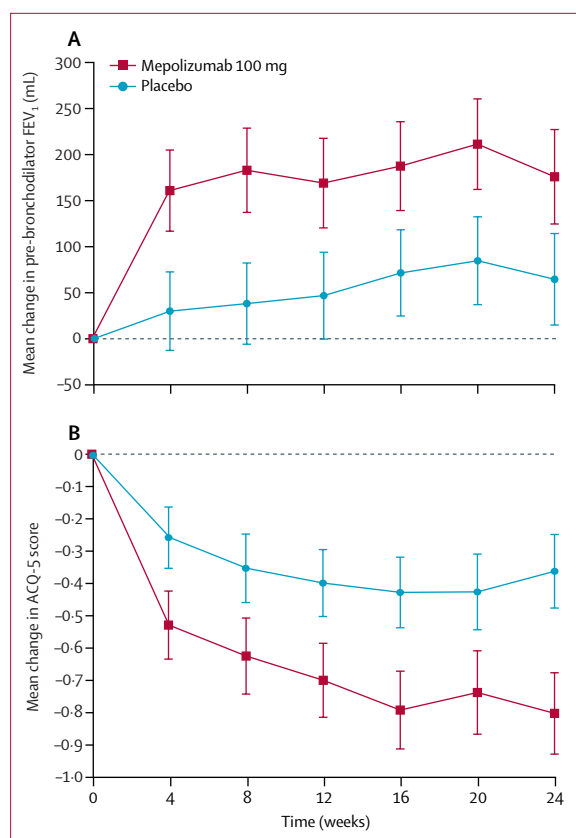


Figure 4: Secondary endpoints at each visit

Data are adjusted mean changes (95% CI) from baseline in (A) pre-bronchodilator FEV₁ and (B) Asthma Control Questionnaire (ACQ)-5 scores.

Furthermore, patients with severe asthma might report few symptoms despite a high inflammatory load^{25,26} and potentially not be able to perceive asthma symptoms as assessed by the ACQ-5. Therefore, although both questionnaires have high levels of reliability and validity in patients with asthma,⁷ changes in symptoms attributable to eosinophilic physiology might not be easily detected by questionnaires such as the ACQ-5, which are focused on specific symptoms rather than a range of respiratory experiences. By contrast, the SGRQ, which includes 50 items, has a broader scope and might be more sensitive to changes in HRQOL in this specific patient population. However, the difference in the ability of SGRQ and ACQ-5 to detect clinically significant improvements in HRQOL and asthma control in this study might also be a result of the two questionnaires including different concepts, with the SGRQ having a focus on acute chest symptoms, good days, shortness of breath, and activity limitation, while the ACQ-5 assesses frequency of individual asthma symptoms.

Early and sustained improvements in lung function also occurred with mepolizumab compared with placebo. An early and sustained improvement in pre-bronchodilator FEV₁ is consistent with findings from other studies of anti-interleukin-5 antibodies^{27,28} and

	Placebo (n=277)	Mepolizumab (n=274)	Treatment difference (95% CI; p value)
Pre-bronchodilator FEV ₁ at week 24 (mL)			120 (47–192; p=0.001)
Baseline pre-bronchodilator FEV ₁	1805 (660)	1887 (709)	..
Change from baseline	56 (26) [n=259]	176 (26) [n=264]	..
Pre-bronchodilator FVC at week 24 (mL)			102 (23–181; p=0.012)
Baseline pre-bronchodilator FVC	2993 (913)	3186 (971)	..
Change from baseline	41 (28) [n=259]	143 (28) [n=264]	..
Pre-bronchodilator FEF _{25–75} at week 24 (mL/s)			123 (46–200; p=0.002)
Baseline pre-bronchodilator FEF _{25–75}	998 (659)	1017 (641)	..
Change from baseline	44 (28) [n=259]	167 (28) [n=264]	..
Exacerbations			
Clinically significant exacerbation			0.42 (0.31–0.56; p<0.0001)
Rate per year	1.21	0.51	..
Exacerbations requiring admission to hospital or an ER visit			0.32 (0.12–0.90; p=0.031)
Rate per year	0.10	0.03	..
Exacerbations requiring admission to hospital			0.31 (0.08–1.24; p=0.098)
Rate per year	0.07	0.02	..

Data are mean (SD) for baseline data, least-squares mean (SE) for changes from baseline, or n (%), except where otherwise stated. Treatment differences for exacerbation endpoints are presented as rate ratios. ER=emergency room. FVC=forced vital capacity. FEF_{25–75}=forced expiratory flow at 25–75% of FVC.

Table 3: Efficacy target endpoints in the modified intention-to-treat population

general trends in the MENSA study,¹⁶ in which an increase in pre-bronchodilator FEV₁ occurred at week 4 with mepolizumab. However, a large placebo effect also occurred in MENSA, obscuring treatment effects, particularly between weeks 8 and 24. The mitigation of such an effect in MUSCA might be attributed to the use of centralised spirometry procedures, reducing the potential for interstudy site variability. Importantly, mepolizumab improved lung function (compared with placebo), unlike other therapies for patients with severe eosinophilic asthma, which are often ineffective in improving lung function because of the lower plasticity of smooth muscle in this population, generally characterised by high levels of airways remodelling.²⁹

In previous studies, greater improvements in outcome measures, such as reductions in exacerbation frequency, have been shown for mepolizumab treatment with increasing baseline blood eosinophil counts in patients with severe eosinophilic asthma.³⁰ This finding is reflective of the higher baseline exacerbation frequency associated with higher baseline blood eosinophil counts, giving patients with higher baseline blood eosinophils more scope for improvement. By contrast, in this study, changes in SGRQ total score were similar across different baseline eosinophil counts, potentially reflecting the equally poor HRQOL at baseline across the range of baseline blood eosinophil counts (data not shown). Conversely, predicted mepolizumab treatment effects for exacerbation rates, pre-bronchodilator FEV₁, and ACQ-5 tend to increase with baseline blood eosinophil counts.

	Placebo (n=278)	Mepolizumab (n=273)
All adverse events		
On-treatment	207 (74%)	192 (70%)
Treatment-related	25 (9%)	31 (11%)
Leading to treatment discontinuation or study withdrawal	3 (1%)	2 (<1%)
All serious adverse events		
On-treatment	22 (8%)	15 (5%)
Fatal	0	0
Adverse events occurring in ≥5% of patients		
Headache	59 (21%)	45 (16%)
Nasopharyngitis	46 (17%)	31 (11%)
Back pain	18 (6%)	13 (5%)
URTI	14 (5%)	17 (6%)
Arthralgia	18 (6%)	9 (3%)
Asthma	15 (5%)	8 (3%)
Systemic or injection-site reactions*		
Systemic reactions	2 (<1%)	2 (<1%)
Injection site reactions	6 (2%)	7 (3%)
Anaphylaxis	1 (<1%)	0
Cardiovascular adverse events†		
Arrhythmias	6 (2%)	2 (<1%)
DVT	0	1 (<1%)

URTI=upper respiratory tract infection. DVT=deep venous thrombosis.
 *As identified in electronic case report forms (eCRF) designed for collecting data about systemic reactions and local injection site reactions. †Data for cardiovascular adverse events are based on investigator completion of the specific page of the eCRF for a predefined list of cardiovascular events: myocardial infarction or unstable angina, congestive heart failure, arrhythmias, valvulopathy, pulmonary hypertension, cerebrovascular events or stroke and transient ischaemic attack, peripheral arterial thromboembolism, and DVT or pulmonary embolism.

Table 4: Summary of adverse events and serious adverse events

These results are in line with a recent post-hoc analysis of the DREAM and MENSA studies, which showed a close relationship between baseline blood eosinophil count and clinical efficacy of mepolizumab.³⁰ The effect of baseline blood eosinophil count on SGRQ differs from the slight correlation between baseline blood eosinophil count and improvement in SGRQ in MENSA.³⁰ This difference perhaps relates to the self-reported nature of the SGRQ score, and the focus on SGRQ as the primary endpoint in MUSCA. In a population with severe asthma, HRQOL is of great importance and might be perceived differently to changes in objective variables such as exacerbation rate and lung function. Nonetheless, given that exacerbation rates and pre-bronchodilator FEV₁ tended to improve with higher baseline blood eosinophil counts, these data support the blood eosinophil thresholds used to identify patients likely to benefit from treatment with mepolizumab, and indicate that continued study of the eosinophil-HRQOL response relationship for all interleukin-5 pathway biologicals is warranted. The safety profile of mepolizumab in this study was similar to that in previous studies of patients

with severe eosinophilic asthma, and was also similar to that of placebo.^{15–17}

To our knowledge, this is the first study to assess HRQOL as the primary endpoint, at several timepoints, in patients with severe eosinophilic asthma, comparing mepolizumab with placebo in addition to standard of care. This study provides valuable new evidence to help understand the effect of mepolizumab on the daily life of patients in this population. Additionally, these results build upon, and are consistent with, results from previous studies.^{15,16} To determine an early predictor of treatment response that identifies patients who are likely to benefit from continued therapy is an important goal to ensure an appropriate risk–benefit ratio with ongoing treatment and to assist in the allocation of resources in short supply. In the case of mepolizumab, an early assessment that ultimately predicts which patients are likely to achieve a reduction in exacerbations would be of particular interest but this is beyond the scope of the current study. Our results suggest that the disease activity instrument used in future studies to explicitly address this question needs to be carefully considered.

One limitation of this study was that, although the treatment difference in SGRQ total and domain scores significantly favoured mepolizumab over placebo at week 24, the change from baseline for placebo also exceeded the MCID for these scores at week 24. This result could have been potentially due to patients in the placebo group receiving frequent monitoring and adhering to their standard of care medications better under clinical trial conditions. However, documentation of consistent therapy in the months before screening was required to reduce changes in adherence during the study. Patient characteristics, including the exclusion of current smokers, and the high degree of reversibility in this population, were generally consistent with previous studies, although they might restrict generalisability to the overall population. Another limitation of this trial was the short length of treatment and assessment compared with previous mepolizumab studies. Although useful and significant results occurred within the 24-week study period, and are consistent with observations over 32 weeks in MENSA,¹⁶ real-world studies to investigate the long-term effects of mepolizumab in patients with severe eosinophilic asthma over a longer period would further increase understanding of the duration of effect.

Finally, we can only speculate about the reasons behind the difference in SGRQ and ACQ-5 scores. However, further assessments, such as the measurement of static or dynamic lung volumes, in addition to the lung function measurements undertaken in the present study, could be done to determine if potential beneficial effects of mepolizumab on small airways disease contribute to the overall improvements in the SGRQ results.

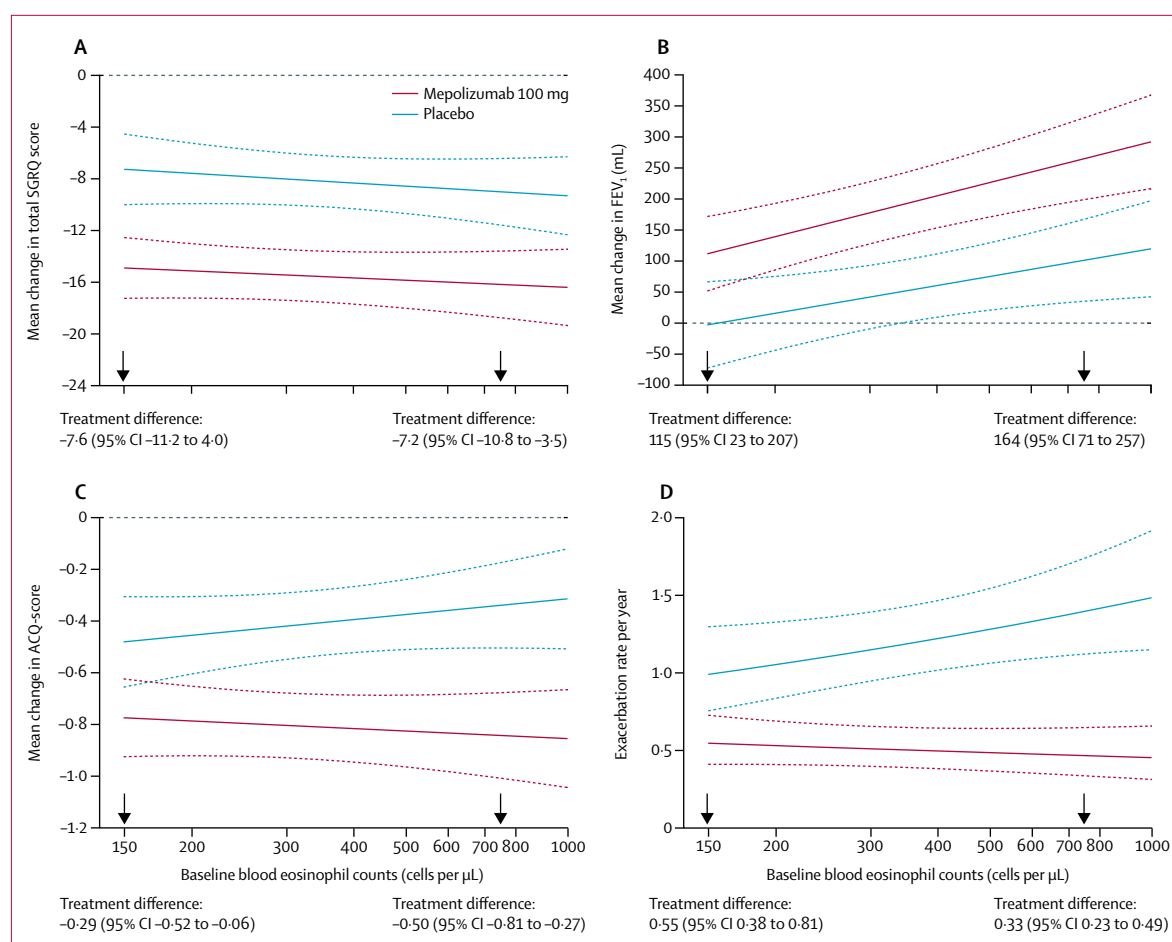


Figure 5: Predictive changes from baseline in target endpoints

Data are adjusted predicted mean changes (95% CI) from baseline in (A) total SGRQ scores, (B) pre-bronchodilator FEV₁, and (C) Asthma Control Questionnaire (ACQ)-5 scores, and (D) predicted mean (95% CI) annual exacerbation rates, by baseline blood eosinophil counts. Data adjusted for the same covariates used in the main analysis. Solid lines represent predicted mean changes from baseline. Dashed lines represent the 95% CI upper and lower bounds. Treatment differences are shown at 150 and 750 cells per µL.

In conclusion, results from the MUSCA study showed significant and clinically relevant, early and sustained improvements in HRQOL, lung function and, in part, asthma symptom control for mepolizumab compared with placebo in patients with severe eosinophilic asthma. These results add to and support the use of mepolizumab as a favourable add-on treatment option to standard of care in this patient population.

Contributors

GLC, JLT, AM, and AtB contributed to data acquisition, and data analysis and interpretation. FCA, LMN and ESB contributed to the study concept, design, analysis, and interpretation. JW-J and DJB contributed to analysis and interpretation. All authors were involved in the preparation and review of the manuscript and approved the final version to be submitted.

Declaration of interests

GLC has acted as a consultant for AstraZeneca, Genentech, Boehringer Ingelheim, and Teva, attended a speaker's bureau with AstraZeneca, Genentech, and Circassia, and received research grants from AstraZeneca and institutional grants from AstraZeneca, Genentech,

Boehringer Ingelheim and GlaxoSmithKline (GSK). ESB, FCA, DJB, JW-J, and LMN are employees at GSK and own GSK stocks or shares. JLT has acted as a consultant for GSK and Boehringer Ingelheim, and has received institutional grants from Novartis and AstraZeneca. AM has received personal fees and non-financial support from GSK, Novartis, Boehringer Ingelheim, AstraZeneca, Stallergenes, ALK, MundiPharma, Teva, Menarini and Meda Pharma. AtB is a member of research boards of GSK, Novartis, and AstraZeneca, and has received independent research grants from GSK and Teva.

Acknowledgments

This study was funded by GlaxoSmithKline (GSK; NCT02281318). Editorial support (in the form of writing assistance, including development of the initial draft based on author direction, assembling tables and figures, collating authors' comments, grammatical editing and referencing) was provided by Thomas Driver (Fishawack Indicia, Cheshire, UK) and Alex Lowe (Fishawack Indicia, Oxford, UK) and was funded by GSK.

References

- 1 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2016. http://ginasthma.org/wp-content/uploads/2016/04/GINA-2016-main-report_tracked.pdf (accessed Feb 18, 2017).

- 2 Arpinelli F, Carone M, Riccardo G, Bertolotti G. Health-related quality of life measurement in asthma and chronic obstructive pulmonary disease: review of the 2009–2014 literature. *Multidiscip Respir Med* 2015; **11**: 5.
- 3 Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet* 2006; **368**: 804–13.
- 4 Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; **43**: 343–73.
- 5 Calhoun WJ, Haselkorn T, Miller DP, Omachi TA. Asthma exacerbations and lung function in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2015; **136**: 1125–27.e4.
- 6 Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; **145**: 1321–27.
- 7 Sanjuas C, Alonso J, Prieto L, Ferrer M, Broquetas JM, Anto JM. Health-related quality of life in asthma: a comparison between the St George's Respiratory Questionnaire and the Asthma Quality of Life Questionnaire. *Qual Life Res* 2002; **11**: 729–38.
- 8 Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; **180**: 59–99.
- 9 Wright A, Hannon J, Hegedus EJ, Kavchak AE. Clinimetrics corner: a closer look at the minimal clinically important difference (MCID). *J Man Manip Ther* 2012; **20**: 160–66.
- 10 Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J* 2002; **19**: 398–404.
- 11 Wyrwich KW, Norquist JM, Lenderking WR, Acaster S. Methods for interpreting change over time in patient-reported outcome measures. *Qual Life Res* 2013; **22**: 475–83.
- 12 Nelsen L, Kimel K, Murray L, et al. Qualitative evaluation of the St George's Respiratory Questionnaire in patients with severe asthma. *Respir Med* 2017. <http://www.sciencedirect.com/science/article/pii/S0954611117300434>.
- 13 GlaxoSmithKline. Mepolizumab (NUCALA) US prescribing information. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL.PDF (accessed Feb 18, 2017).
- 14 GlaxoSmithKline UK. Mepolizumab (NUCALA) EU summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003860/WC500198037.pdf (accessed Feb 18, 2017).
- 15 Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; **380**: 651–59.
- 16 Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; **371**: 1198–207.
- 17 Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; **371**: 1189–97.
- 18 GlaxoSmithKline. A randomised, double-blind, placebo-controlled, parallel-group, multi-centre 24-week study to evaluate the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe eosinophilic asthma on markers of asthma control. <https://www.gsk-clinicalstudyregister.com/study/200862#ps> (accessed Feb 18, 2017).
- 19 Cope S, Donohue JF, Jansen JP, et al. Comparative efficacy of long-acting bronchodilators for COPD: a network meta-analysis. *Respir Res* 2013; **14**: 100.
- 20 Siler TM, Donald AC, O'Dell D, Church A, Fahy WA. A randomized, parallel-group study to evaluate the efficacy of umecclidinium/vilanterol 62.5/25 µg on health-related quality of life in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2016; **11**: 971–79.
- 21 Singh D, Ferguson GT, Bolitschek J, et al. Tiotropium + olodaterol shows clinically meaningful improvements in quality of life. *Respir Med* 2015; **109**: 1312–19.
- 22 Cloutier MM, Schatz M, Castro M, et al. Asthma outcomes: composite scores of asthma control. *J Allergy Clin Immunol Pract* 2012; **129** (3 suppl): S24–33.
- 23 Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008; **178**: 218–24.
- 24 Barnes PJ. Therapeutic approaches to asthma-chronic obstructive pulmonary disease overlap syndromes. *J Allergy Clin Immunol Pract* 2015; **136**: 531–45.
- 25 Barbaro MP, Lacedonia D, Palladino GP, et al. Dyspnea perception in asthma: role of airways inflammation, age and emotional status. *Respir Med* 2011; **105**: 195–203.
- 26 Veen JC, Smits HH, Ravensberg AJ, Hiemstra PS, Sterk PJ, Bel EH. Impaired perception of dyspnea in patients with severe asthma. Relation to sputum eosinophils. *Am J Respir Crit Care Med* 1998; **158**: 1134–41.
- 27 Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med* 2014; **2**: 879–90.
- 28 Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015; **3**: 355–66.
- 29 Homer RJ, Elias JA. Airway remodeling in asthma: therapeutic implications of mechanisms. *Physiology (Bethesda)* 2005; **20**: 28–35.
- 30 Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med* 2016; **4**: 549–56.