Single Technology Appraisal

Mepolizumab for treating severe eosinophilic asthma [ID798]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Mepolizumab for treating severe eosinophilic asthma [ID798]

Appraisal Committee Meeting – 2 March 2016

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Mepolizumab for treating severe refractory eosinophilic asthma

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The marketing authorisation for mepolizumab states that it is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults. How is severe, refractory, eosinophilic asthma defined in clinical practice? Would these patients receive systemic corticosteroids?
- The marketing authorisation does not specify a baseline blood eosinophil count criteria for treatment with mepolizumab. The company stated that baseline blood eosinophil count was the strongest predictor of treatment response and included a threshold of ≥150/μL in its proposed population. The ERG queried why a threshold of ≥300/μL in the previous 12 months did not improve treatment response. Clinical advisors to the ERG stated that a threshold of 300/μL in the

previous 12 months would be more suitable. Does the committee consider that the threshold blood eosinophil count suggested by the company is appropriate?

- The company's undertook post-hoc modelling to identify a proposed population, that is people with a baseline blood eosinophil count of ≥150/μ, and there are differences in the baseline characteristics compared with the ITT populations. Is the committee satisfied that this 'proposed population' should form the basis of its decision-making?
- The company's proposed population includes people receiving systemic corticosteroids regardless of number of exacerbations in the previous year because it represents a population with very severe disease regardless of number of exacerbations. Nonetheless the company highlighted that exclusion of systemic steroid users with <4 exacerbations in the previous year would result in additional clinical and cost-effectiveness benefit for mepolizumab. Does the Committee agree that the population under consideration should include people receiving systemic corticosteroids with <4 exacerbations in the previous year?
- The recommended dose of mepolizumab is 100 mg administered subcutaneously. However, the trials are based on 75mg IV and 100mg subcutaneous mepolizumab and the company also presented pooled results incorporating both doses and administration methods. The 2 doses were deemed bioequivalent by the EMA. Does the committee consider that the evidence for 75mg IV mepolizumab can be generalised to 100mg subcutaneous mepolizumab?
- Omalizumab is a comparator for a small overlap population. The company's preferred approach to identifying this population was to include all omalizumab eligible patients (with ≥1 systemic corticosteroid treated exacerbations in the previous year) and all mepolizumab eligible patients irrespective of whether they are omalizumab eligible (with ≥2 systemic corticosteroid treated exacerbations in the previous year), based on the modified ITT population. Does the committee consider this approach to be appropriate?
- Only a small proportion of patients in the mepolizumab and omalizumab trials were eligible for both treatments, and study populations differed in terms of severity. Does the committee consider the results from this analysis to be sufficiently robust?

- The ERG stated that because of heterogeneity between studies, network-meta analysis results for mepolizumab compared with omalizumab from the random effects model are more appropriate. What is the committee's view?

Cost-effectiveness

- What is the most appropriate population for inclusion in the model The modified intention-to-treat (ITT) population (all trial patients who were randomised and received at least one dose of study medication), the company proposed population (blood eosinophil count of 150 cells/μl at initiation of treatment and 4 or more exacerbations in the previous year or were dependent on systemic corticosteroids) the company restricted population (blood eosinophil count of 150 cells/μl at initiation of treatment and 4 or more exacerbations in the previous excluding people on maintenance corticosteroids with <4 exacerbations)
- Does the committee consider that a 10 year treatment duration in the model is appropriate or is lifetime treatment duration more reflective of clinical practice in England?
- Does the committee consider that utility estimates based on EQ-5D data from the trials are more appropriate that mapping from SGRQ to EQ-5D? Does the committee consider that the length of utility decrements for exacerbations from the MENSA trial to be more appropriate than the estimates from the Lloyd study?
- Does the committee consider that the assumptions around continuation criteria (that is people treated with mepolizumab continued on treatment unless the exacerbation rate worsened compared with the previous year) in the model are appropriate? Does the committee consider the assumption that the effect of treatment with mepolizumab will remain the same throughout the duration of the model to be appropriate?
- What does the committee consider to be the most appropriate sources for exacerbation rates in the model, the MENSA trial where exacerbation rates were measured shortly after initiation of mepolizumab treatment or the COSMOS extension study where rates of exacerbation were measured for a full year in patients who had already been on mepolizumab for 32 weeks?

- What does the committee consider to be the most appropriate source for asthma related mortality in the model, the WATSON study where asthma mortality was measured in age bands18 to 44 years and 45 years and over, therefore assuming a constant rate of asthma-related mortality for people aged 45 years and over, or the Roberts study which stratified patients into narrower age bands including for people aged 65 years?
- Which of the ERG exploratory analyses does the committee prefer?

1 Remit and decision problem

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of mepolizumab within its marketing authorisation for treating severe eosinophilic asthma.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the base case	Company comments	ERG comments
Population	Adults with severe eosinophilic asthma	Adults with severe refractory eosinophilic asthma with a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or dependency on maintenance oral corticosteroids mOCS.	A more severe sub-population of the anticipated licensed indication, mindful of NHS resources and current NHS implementation of NICE guidance for omalizumab .	• Population in the scope and the company submission is "severe eosinophilic asthma", but the marketing authorisation for mepolizumab is for "severe **refractory** eosinophilic asthma" • It is unclear how to define the relevant population in terms of extent of asthma severity and extent of eosinophilia. These are not explicitly defined in the scope or the marketing authorisation • Concern that company's proposed population is based on modelling post hoc analyses.
Intervention	Mepolizumab (in addition to best standard care)	As per scope	N/A	Consistent with the NICE scope
Comparators	1. Best standard care without	As perscope	N/A	Consistent with the NICE

	mepolizumab 2. For people with severe persistent allergic **IgE-mediated eosinophilic** asthma: • Omalizumab			scope
Outcomes	• Control of asthma • incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation • use of oral corticosteroids • patient and clinician evaluation of response • lung function • mortality • time to discontinuation • adverse effects of treatment • health-related quality of life.	As per scope	N/A	Consistent with the NICE scope

2 The technology and the treatment pathway

2.1 Asthma is a chronic inflammatory respiratory disease associated with variable airflow obstruction and airway hyper-responsiveness. It is characterised by exacerbations associated with symptoms such as breathlessness, chest tightness, wheezing, sputum production and cough. Allergic asthma is known as 'IgE mediated' asthma. Severe eosinophilic asthma is a subset of asthma that is characterised by eosinophils in both blood and sputum and by recurrent exacerbations. Eosinophilia can occur without increased IgE. Eosinophils play a major role in airway inflammation in asthma.

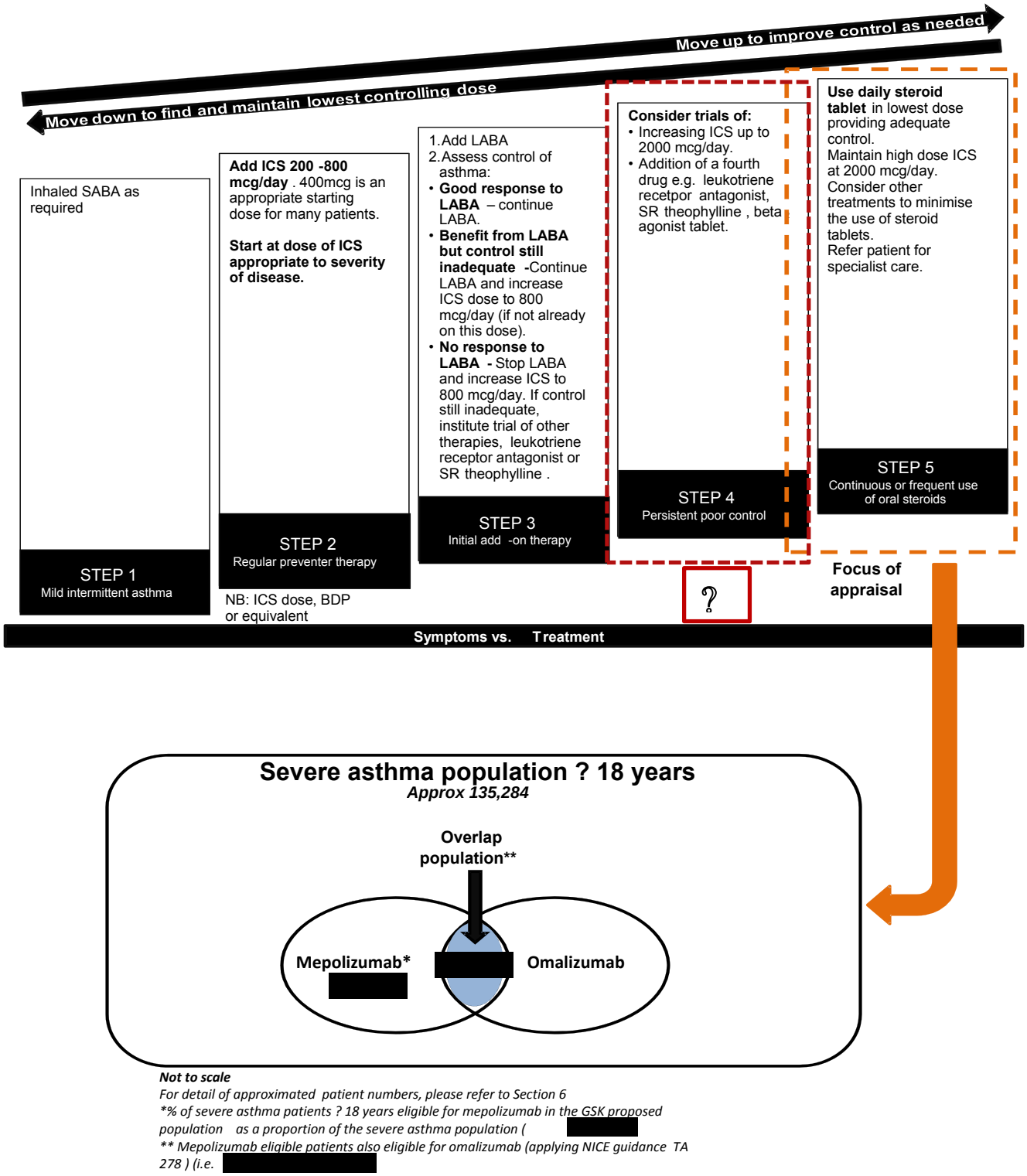
2.2 Current British guidelines from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) recommend a stepwise approach to treatment in adults. Control is achieved and maintained by stepping up treatment as necessary and stepping down when control is good. The guideline steps are as follows:

- Step 1. Inhaled short-acting beta-2 agonist as required.
- Step 2. Add inhaled corticosteroid (200–800 micrograms per day).
- Step 3. Add an inhaled long-acting beta-2 agonist. If control remains inadequate, increase the dose of the inhaled corticosteroid to 800 micrograms per day. If there is no response to the inhaled long-acting beta-2 agonist, stop this drug and increase the inhaled corticosteroid dose 800 micrograms per day. If control is still inadequate, try a leukotriene receptor antagonist or slow-release theophylline.
- Step 4: Consider increasing the dose of inhaled corticosteroid up to 2000 micrograms per day. Consider adding a fourth drug (for

example, a leukotriene receptor antagonist, slow-release theophylline or a beta-2 agonist tablet).

- Step 5: Use daily corticosteroid tablets at the lowest dose providing adequate control. Maintain high-dose inhaled corticosteroid at 2000 micrograms per day. Consider other treatments to minimise the use of steroid tablets. Refer patients to specialist care.

Figure .1 Treatment pathway from British guideline on the management of asthma. British Thoracic Society and Scottish Intercollegiate Guidelines Network (October 2014) (company submission page 27)



Not to scale
For detail of approximated patient numbers, please refer to Section 6
**% of severe asthma patients ? 18 years eligible for mepolizumab in the GSK proposed population as a proportion of the severe asthma population ([redacted]*
*** Mepolizumab eligible patients also eligible for omalizumab (applying NICE guidance TA 278) (i.e. [redacted]*

2.3 NICE technology appraisal guidance 278 recommends omalizumab as an option for treating severe persistent allergic IgE-mediated asthma as add-on therapy to optimised standard therapy in people aged 6 years and older who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year), and only if the company makes omalizumab available with the discount agreed in the patient access scheme.

2.4 The company stated that people with severe refractory asthma are typically under Step 4 or Step 5, but indicated that the population in step 5 is the focus of this appraisal. The ERG noted that the comparators in the scope are in line with Step 4 or Step 5 of the guidelines.

Table 2 The technologies

	Mepolizumab (GSK)	**Omalizumab (Novartis)**	Best standard care without mepolizumab
Marketing authorisation	Indicated as an add-on treatment for severe refractory eosinophilic asthma in adults	Indicated as add-on therapy to improve control of asthma in adults and adolescents 12 years and over and children aged 6 to 11 years with severe persistent allergic asthma who have: • a positive skin test or in vitro reactivity to a perennial aeroallergen • reduced lung function (forced expiratory volume at 1 second [FEV1] less than 80% (in adults and adolescents) • frequent daytime symptoms or night-time awakenings • multiple documented severe exacerbations despite daily high-dose inhaled corticosteroids plus a long-acting inhaled beta2 agonist. The marketing	N/A

		authorisation states that omalizumab treatment 'should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma'.	
Dosage and administration method	100 mg administered (subcutaneous injection) every 4 weeks	75–600 mg administered (subcutaneous injection) every 2 or 4 weeks, up to a maximum dosage of 600 mg every 2 weeks. Exact dosing depends on serum IgE and weight.	N/A
Cost (excluding VAT).	UK list price is £840.00 per dose/cycle. The company has agreed a confidential patient access scheme with the Department of Health which results in a price of [redacted]	UK list price is £256.15 for a 150-mg vial and £128.07 for a 75-mg vial. The company explores costs of £617.99 per cycle (based on dosing in TA 278) and £872.22 (based on IMS Health data) in its submission. There is a confidential patient access scheme reducing the cost to [redacted] per cycle (based on TA278).	Estimated to be £56.84 per cycle

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 The patient expert submission included a summary of responses from a survey of approximately 50 patients with severe asthma. These comments highlighted that severe asthma is distressing and socially isolating. Patients often cannot breathe well enough to walk or go to work, and live in fear because ordinary factors like dust, fragrances or a common cold can trigger a life threatening attack. This results in a substantial psychological and economic burden for patients.

3.2 The clinical experts stated that eosinophilic asthma is the most severe form of asthma and the most difficult to treat. The clinical expert noted that while corticosteroids were very effective, they were associated with

long-term complications, and that corticosteroid sparing treatments were urgently needed. The expert noted that mepolizumab would likely be given to people characterised by stage 4 or 5 of the British Thoracic Society criteria with eosinophilia, but that it was not clear what level of eosinophilia would be appropriate. The clinical expert also noted that patients should be phenotyped not only on the basis of eosinophilia, but also from eosinophils obtained from sputum or from bronchoalveolar lavage because mepolizumab is likely to be most effective in people with increased levels of eosinophils both in their blood and in their airways. The expert noted that the more eosiophilic patients are the more likely they are to benefit. Finally, clinical experts noted that if mepolizumab is prescribed, clinicians will need to establish compliance with inhaled treatment.

3.3 Patient experts highlighted that severe eosinophilic asthma does not respond to standard treatment and requires more intensive and expensive therapies to control symptoms to prevent attacks, hospitalisations and deaths.

3.4 With regard to availability, the clinical experts stated that they expect mepolizumab to be used only in the specialists setting because of the high cost of the drug and because clinicians in tertiary care can phenotype patients, and have experience managing severe asthma. No additional resources or staff training in specialist centres is expected unless the definition of eosinophilic asthma requires broncoalveolar lavage.

4 Clinical-effectiveness evidence

4.1 The company conducted a systematic literature review and identified 3 key randomised controlled trials: DREAM, MENSA and SIRIUS. The company also provided supportive evidence from early studies (SB-240563/006, CRT110184, and SB-240563/046), and extension studies (COLUMBA and COSMOS).

4.2 MENSA (n=576) was a multicentre (including UK), phase III, randomised, double-blinded trial that compared mepolizumab (100mg or 75mg once every 4 weeks) with placebo for 32 weeks. The population included people aged 12 years and older with severe refractory eosinophilic asthma on high dose oral corticosteroids and a history of 2 or more exacerbations in the previous 12 months. All people in the trial had a blood eosinophil level of >300 cells/μL in the 12 months prior to screening or >150 cells/μL at screening. Eosinophil count is a blood test that measures the quantity of the white blood cell eosinophils in the body. In clinical practice, a normal blood sample reading will show fewer than 350 eosinophil cells per microliter of blood).

4.3 DREAM (n=616) was a multicentre (including UK) phase IIb, randomised, double blind trial comparing mepolizumab (75mg, 250mg and 750mg once every 4 weeks) with placebo for 52 weeks. The inclusion criteria was similar to MENSA, including people aged 12 years and older with severe refractory eosinophilic asthma on high dose oral corticosteroids and a history of 2 or more exacerbations in the previous 12 months. However, eosinophilic airway inflammation could be demonstrated by elevated blood eosinophils of ≥300 cells/μL; elevated sputum eosinophils of ≥3%; elevated fractional exhaled nitric oxide (FeNO) of ≥50 ppb; or deteriorating asthma control after reducing the maintenance dose of either inhaled corticosteroids or oral corticosteroids by ≤25% in the previous 12 months.

4.4 SIRIUS (n=135) was a multicentre (including UK), phase III, randomised, double-blinded trial that compared mepolizumab 100mg once every 4 weeks, with placebo for 24 weeks. The population included people aged 12 years and older with severe eosinophilic asthma who required regular treatment with maintenance systemic corticosteroids and high-dose inhaled corticosteroids. All patients in the trial had a blood eosinophil level of >300 cells/μL in the 12 months prior to screening or >150 cells/μL at screening. The study included an initial phase in which

patients had their corticosteroids optimised; only patients on a stable dose of corticosteroids were randomised.

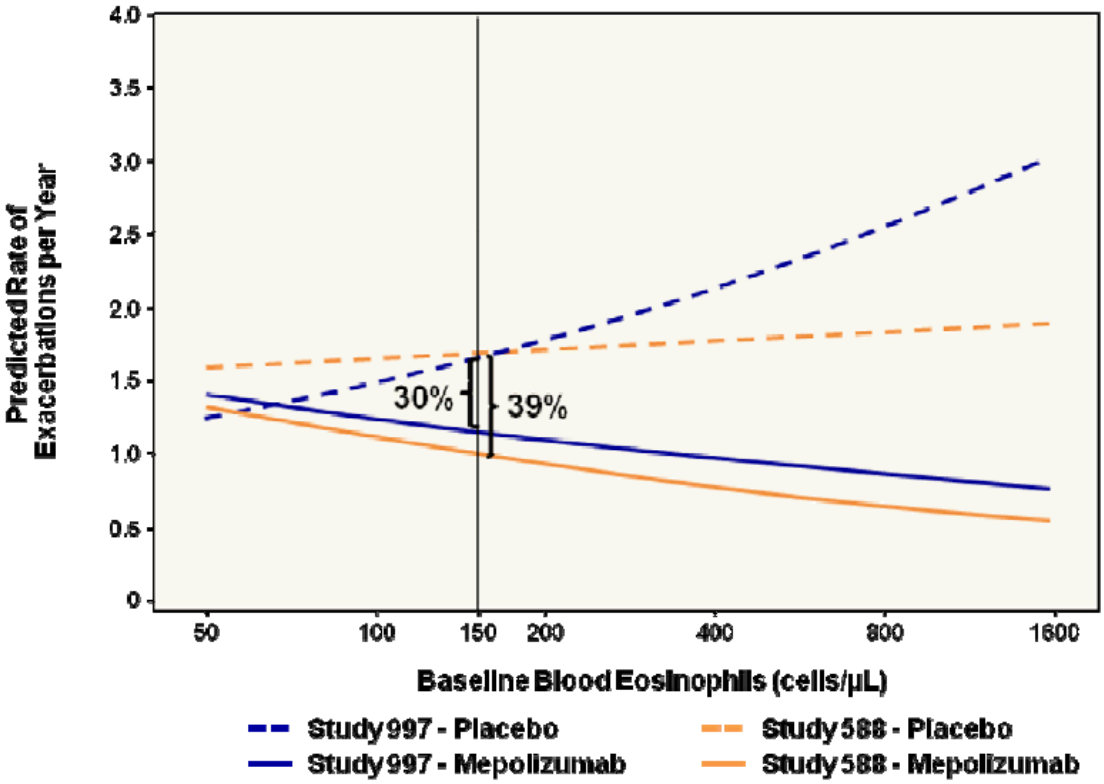
4.5 The primary outcome in MENSA and DREAM was the reduction of clinically significant exacerbations of asthma, defined by worsening of asthma which required use of systemic corticosteroids and/or hospitalisation and/or emergency department visits. People did not have to be treated with systemic corticosteroids at the start of the trials. The primary outcome in SIRUS was the reduction in use of oral corticosteroids during weeks 20 to 24 compared with baseline (see ERG report table 5, page 38).

4.6 The company presented clinical and cost-effectiveness results for the population termed the modified intention-to-treat (ITT), that is, all trial patients who were randomised and received at least one dose of study medication. The company did no interim analyses other than for safety. To test the efficacy of mepolizumab for clinically significant exacerbations, the company analysed the data using a negative binomial model adjusting for treatment group, baseline maintenance oral corticosteroids (yes vs. no), region, exacerbations in the year prior to the study and baseline % predicted (pre-bronchodilator) forced expiratory volume in 1 second (FEV_1). with time on treatment as an offset variable to denote the exposure period. The company included data for patients who withdrew up to the time of withdrawal; for missing data thereafter, the company assumed that 'future' exacerbations for those who withdraw can be predicted from their rates of exacerbation prior to withdrawal and from patients on the same treatment. The company controlled for multiple testing. The company also analysed mepolizumab's effect on the rate of exacerbations requiring hospitalisation or emergency department visits. As the primary endpoint of SIRIUS was decrease in corticosteroid use rather than rate of exacerbation, the company analysed mepolizumab's effect on the reduction of daily oral steroid dose during weeks 20-24 compared to dose determined during optimisation phase adjusted for region, number

of years on oral steroids (<5 years versus ≥5 years), and baseline oral steroid dose. .

4.7 The company stated that subgroups with more severe disease were likely to benefit more from treatment with mepolizumab and presented results. The company defined the subgroups via post-hoc modelling and subgroup analyses of DREAM and MENSA. The company carried out multivariate analysis to identify which people had the most frequent number of exacerbations with the goal of limiting analyses to these people. The covariates considered were gender, age, weight, region, baseline % predicted FEV1, airway reversibility, number of exacerbations in the previous year, baseline blood eosinophil count, baseline use of maintenance oral corticosteroids, and IgE level. The company stated that baseline blood eosinophil count most strongly predicted treatment response. Figure 2 shows that in the post hoc modelling analysis of people with a blood eosinophil count of ≥150 cells/μl when starting treatment, the DREAM trial indicated a 30% or more reduction in exacerbations for mepolizumab compared with placebo and the MENSA trial indicated a 39% or more reduction in exacerbations for mepolizumab compared with placebo. Additional predictive modelling showed that patients with a higher historic exacerbation rate (≥4 in the previous 12 months) experienced a greater numerical reduction in exacerbations per annum than those with fewer exacerbations (<4).

Figure 2: Predicted rate of exacerbations by baseline blood eosinophil count in the ITT populations of DREAM (Study 997) and MENSA (Study 588) (source Figure 7 on page 77 of the company submission).



4.8 Based on these results, the company proposed a preferred population for its base-case analysis: adults with severe refractory eosinophilic asthma with a blood eosinophil count of ≥150 cells/µL at initiation of treatment; and ≥4 exacerbations in the previous year and/or dependency on systemic corticosteroids (regardless of number of exacerbations). The company stated that although the modified ITT population is likely to benefit from mepolizumab irrespective of eosinophil levels, the benefits will be greater in the company's chosen subgroup and will ensure an efficient use of NHS resources. The company stated that clinical experts considered that they could identify these patients, and that these patients were representative of the UK population severe refractory eosinophilic asthma.

4.9 The company stated that people who receive systemic corticosteroids represent a population with very severe disease and therefore should be included regardless of how many exacerbations they have had in previous year. However, the company highlighted that benefits of reducing corticosteroid exposure are not fully captured in clinical and

cost-effectiveness analyses. The company separately presented results for people with a blood eosinophil count of ≥150 cells/μL at initiation of treatment and ≥4 exacerbations in the previous year and/or dependency on systemic corticosteroids (regardless of exacerbations) (its proposed population), and its proposed population excluding those on systemic corticosteroids with <4 exacerbations in the previous year. Additionally, in response to a request by the ERG, the company also presented results for people with a blood eosinophil count of ≥150 cells/μL at initiation of treatment and on systemic corticosteroids with <4 exacerbations in the previous year.

ERG comments

4.10 The ERG stated that the committee should interpret with caution the post- hoc modelling analysis used to identify the company's proposed population. The ERG noted that its clinical advisors agreed that a threshold of ≥4 previous exacerbations was appropriate. However, they questioned a blood eosinophil threshold of ≥150/μL, because it is a relatively low count within the normal range, and because eosinophil levels can fluctuate. Instead, the advisors suggested a blood eosinophil threshold of 300/μL in the previous 12 months. The ERG noted that the European Medicines Agency stated that eosinophil levels were not sufficiently predictive to justify a specific cut-off within the marketing authorisation for mepolizumab. The ERG highlighted that the post hoc modelling analysis showed that when using a threshold of ≥300/μL in previous 12 months, the reduction in exacerbations was smaller for those with ≥300/μL, which is counter-intuitive (see figure 2 above). The ERG therefore questioned whether the findings for the ≥150/μL threshold may be due to chance or confounding. .

4.11 The ERG was satisfied that the company included all relevant studies in its submission. The ERG noted that the duration of the trials were relatively short at 24 to 52 weeks. The ERG questioned the extent to which SIRUS reflected clinical practice in England because the trial excluded patients if they were not able to achieve a stable dose of oral

corticosteroids. The ERG also noted that the primary outcome in DREAM and MENSA (clinically significant exacerbations) was a composite outcome which includes using systemic corticosteroids (or double maintenance dose) and/or hospitalisation and/or hospital emergency department visits. The ERG noted that loss to follow-up between treatment groups and the proportion of patients withdrawing because of adverse events was similar across treatment groups in all of the trials.

4.12 The ERG noted the company's comment that that there were no important differences in patient demographic and baseline characteristics between treatment groups in DREAM and MENSA for the ITT population (see page 66 of the company's submission for further details), but the ERG noted that data was provided for the whole trial, rather than by treatment group. The ERG noted that there were some differences between treatment groups in the SIRIUS ITT population, for example gender and duration of asthma. However it stated that there were no differences in patient characteristics which consistently favoured a particular treatment group.

4.13 All 3 trials reported data on clinically significant exacerbations with or without hospitalisation). The results for intravenous mepolizumab 75mg compared with placebo from MENSA and DREAM, and for subcutaneous 100mg mepolizumab compared with placebo from SIRIUS and MENSA are reported in table 3 and table 4. The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks. The EMA deemed that this was bioequivalent to 75 mg administered intravenously once every 4 weeks. However, the incidence of injection site reactions is higher for mepolizumab administered subcutaneously (8%) than intravenously (1.7%) but these are non-serious and the majority resolved within a few days; 2 patients withdrew due to injection site reactions. The company presented pooled results from the 75mg IV arm and 100mg SC arms of MENSA to increase the

certainty in the treatment effectiveness and used these pooled results in its meta-analyses and in the model.

4.14 The results show that mepolizumab reduces the rate of clinically significant exacerbations compared with placebo in the ITT populations of all the trials, and that the results were statistically significant. For the company's proposed population, mepolizumab reduced the rate of clinically significant exacerbations compared with placebo in DREAM and MENSA but not in SIRIUS.

Table 3 Results for clinically significant exacerbations for mepolizumab compared with placebo (source: Table 14 on page 51 of the ERG report)

	Modified ITT population Mepolizumab vs.placebo Rate ratio,(95% Confidence interval)	Company proposed population Mepolizumab vs. placebo Rate ratio,(95% Confidence interval)	Company proposed population excluding people on maintenance corticosteroids with <4 exacerbations Mepolizumab vs. Placebo Rate ratio (95 % Confidence interval)
MENSA (75mg) IV	0.53 (0.39 to 0.71)	0.40 (0.24 to 0.67)	0.39 (0.22 to 0.68)
MENSA (100mg) SC	0.47 (0.35 to 0.63)	0.50 (0.32 to 0.78)	0.39 (0.23 to 0.67)
MENSA pooled (75 IV and 100mg SC)	0.50 (0.39 to 0.64)	Not reported	Not reported
DREAM (75mg IV)	0.52 (0.39 to 0.69)	0.36 (0.24 to 0.55)	0.31 (0.18 to 0.53)
SIRIUS (100mg SC)	0.68 (0.47 to 0.99; p value 0.042)	0.77 (0.51 to 1.17;p value 0.222)	0.81 (0.40 to 1.64; pa value 0.556)
DREAM +MENSA (75mg IV or 100mg SC)	0.51 (0.42 to 0.62)	0.41 (0.31 to 0.55)	0.35 (0.25 to 0.50)
DREAM +MENSA+SIRIUS (75mg IV or 100mg SC)	Not possible	0.50 (0.40 to 0.64)	0.42 (0.30 to 0.57)

- The modified intention-to-treat (ITT) population (all trial patients who were randomised and received at least one dose of study medication), the company proposed population (blood eosinophil count of 150 cells/μl at initiation of treatment and 4 or more exacerbations in the previous year or were dependent on systemic corticosteroids)

Table 4 Results for exacerbations requiring hospitalisation for mepolizumab compared with placebo (source: Table 15 on page 54 of the ERG report)

	ITT population Mepolizumab vs.placebo Rate ratio,(95% Confidence interval; p-value)	Company proposed population Mepolizumab vs. placebo Rate ratio,(95% Confidence interval; p-value)	Company proposed population excluding people on maintenance corticosteroids with <4 exacerbations Mepolizumab vs. Placebo Rate ratio (95 % Confidence interval; p-value)
MENSA (75mg IV)	0.61 (0.23 to 1.66)	0.28 (0.05 to 1.45)	0.19 (0.03 to 1.31)
MENSA pooled (100mg SC)	0.31 (0.11 to 0.91)	0.55 (0.15 to 2.03)	0.49 (0.11 to 2.11)
MENSA (75 IV or 100mg SC)	0.44 (0.19 to 1.02)	Not reported	Not reported
DREAM (75 IV mg)	0.61 (0.28 to 1.33)	0.45 (0.14 to 1.43)	0.50(0.13 to 1.97)
DREAM +MENSA (75mg IV or 100mg SC)	0.50 (0.28 to 0.89)	0.44 (0.19 to 1.02)	0.43 (0.16 to 1.12)

- The modified intention-to-treat (ITT) population (all trial patients who were randomised and received at least one dose of study medication), the company proposed population (blood eosinophil count of 150 cells/μl at initiation of treatment and 4 or more exacerbations in the previous year or were dependent on systemic corticosteroids)

4.15 The primary outcome in SIRIUS was the percentage of patients who reduced their corticosteroids dose during weeks 20 to 24 compared with their baseline dose of corticosteroids, while maintaining asthma control. People receiving mepolizumab were more likely to reduce their corticosteroids compared with placebo with an odds ratio of 2.39, (95% CI 1.25 to 4.56) in the modified ITT population, 1.81 (95% CI 0.86, 3.79)

in the company's proposed population and 2.75 (95% CI 0.72, 10.59) in the company's proposed population excluding people on maintenance corticosteroids with <4 exacerbations. None of these results were statistically significant.

4.16 A range of secondary outcomes all reflecting corticosteroid dose reduction was also reported in SIRIUS at week 20 compared to baseline. For example in the company's proposed population 48% of people treated with mepolizumab reduced their corticosteroid dose by at least 50% compared with 38% for placebo (OR 1.60, 95% CI 0.70 to 3.64) and 13% of people treated with mepolizumab stopped taking corticosteroids compared with 8% with placebo (OR 1.35, 95% CI 0.32 to 5.78). For further details see Table 23 on page 63 of the ERG report.

4.17 The company acknowledged that its smaller proposed population may not be adequately powered to find that mepolizumab reduces the occurrence of rarer events, for example exacerbations requiring hospitalisation, but stated that the trend was in line with the modified ITT population results.

Health-related quality of life (HRQoL)

4.18 Health related quality of life was assessed in DREAM using the EQ-5D utility index. EQ-5D data were collected at screening and at 4 weekly intervals until week 52. The mean change from baseline EQ-5D score at Week 52 was 0.07 for placebo and 0.08 for mepolizumab 75mg in the modified ITT population. The company highlighted that at baseline approximately a third of patients in DREAM reported an EQ-5D utility score of 1.0, which does not reflect the impact of severe asthma on the quality of life of this patient population and meant that for this group of patients no improvement in health status was possible as a result of mepolizumab treatment. This is likely because the EQ-5D does not include a recall period. The company also noted that for patients experiencing ≥ 4 exacerbations in the previous 12 months the EQ-5D differential between mepolizumab and placebo was worse than in the

modified ITT population. The company stated that this suggests that EQ-5D is not an appropriate measure in severe asthma. The phase 3 MENSA and SIRIUS trials included the St George's Respiratory Questionnaire (SGRQ), a disease specific questionnaire designed to measure health impairment in patients with asthma. The SGRQ demonstrated statistically significant improvement with mepolizumab in both MENSA and SIRIUS (see ERG report table 18, page 58). The company stated that the minimal clinically important difference for SGRQ is 4 units and the differences in MENSA and SIRIUS range from 5 to 13 units for all 3 populations. The company noted that decrement of quality of life experienced during an exacerbation and fear of an exacerbation would not have been captured in these estimates.

4.19 Additionally, the trials included the Asthma Control Questionnaire (ACQ) measuring the mean change in ACQ score from baseline at the end of the study period. The results are presented in table 5 below. The company stated that the minimum clinically important difference for the ACQ questionnaire is 0.5 and therefore the results indicate that the company's proposed population experiences greater benefit from mepolizumab treatment compared with the modified ITT population.

Table 5 Results for the mean change in ACQ score from baseline (source: Table 19 on page 59 of the ERG report)

	Modified ITT population Mepolizumab vs. placebo Change in ACQ score,(95% Confidence interval)	Company proposed population Mepolizumab vs. placebo Change in ACQ score,(95% Confidence interval)	Company proposed population excluding people on maintenance corticosteroids with <4 exacerbations Mepolizumab vs. Placebo Change in ACQ score (95 % Confidence interval)
MENSA (75mg)	-0.42 (-0.61 to -0.23)	-0.54 (-0.86 to -0.23)	-0.72 (-1.10 to -0.33)
MENSA (100mg)	-0.44 (-0.63 to -0.25)	-0.79 (-1.09 to -0.49)	-0.96 (-1.33 to -0.59)
MENSA pooled	-0.43 (-0.59 to -0.26)	N/R	N/R

(75 and 100mg)			
DREAM (75mg)	-0.16 (-0.39 to -0.07)	-0.17 (-0.65 to 0.30)	-0.47 (-1.09 to 0.16)
SIRIUS (100mg)	-0.52 (-0.87 to -0.17)	-0.65 (-1.06 to -0.24)	-0.88 (-1.71 to -0.05)
DREAM +MENSA (75mg or 100mg)	-0.34 (-0.48 to -0.20)	-0.56 (-0.79 to -0.33)	-0.76 (-1.05 to -0.47)
DREAM +MENSA+SIRIUS (75mg or 100mg)	Not possible	-0.58 (-0.79 to -0.38)	-0.78 (-1.05 to -0.50)

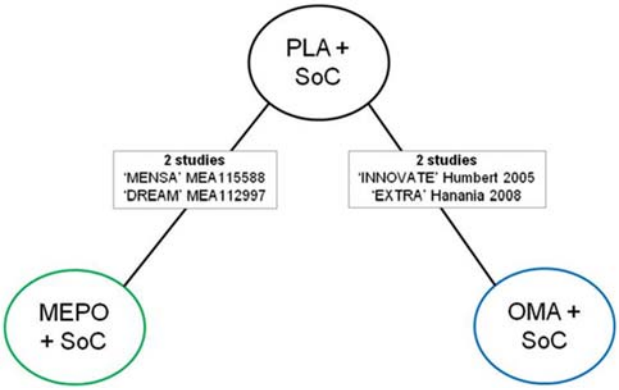
Indirect comparison

4.20 To estimate the effectiveness of mepolizumab compared with omalizumab, the company conducted an indirect treatment comparison, using data from MENSA and DREAM. The company explained that the indirect comparison was only conducted in the modified ITT population as opposed to the company's proposed population, because it did not have access to individual patient data for omalizumab. The company noted that omalizumab was a comparator for a small overlap population of patients who exhibit both allergic (IgE) and eosinophilic phenotypes of severe asthma. The company presented 3 approaches to identify the overlap population (see company submission page 129) and considered that including the full MODIFIED ITT populations for both mepolizumab and omalizumab would be most balanced and inclusive. This includes omalizumab eligible patients (with ≥1 systemic corticosteroid treated exacerbations in the previous 12 months) and all mepolizumab eligible patients irrespective of whether they are omalizumab eligible (with ≥2 systemic corticosteroid treated exacerbations in the previous year).

4.21 In the absence of head-to-head trials comparing mepolizumab and omalizumab, data from the INNOVATE and EXTRA omalizumab trials were used to form a network to compare the treatment effects of mepolizumab, omalizumab and standard of care for three outcomes: (i) clinically significant exacerbations; (ii) exacerbations requiring hospitalisation, and; (iii) change from baseline in predicted FEV1. Separate NMAs were undertaken for each outcome. The INNOVATE

(n=419) and EXTRA (n=850) were a phase 3 randomised, placebo-controlled, double-blind studies comparing omalizumab with placebo. The INNOVATE study included people with inadequately controlled severe persistent allergic asthma and the EXTRA study included people with inadequately controlled moderate to severe asthma. Two additional open-label randomised controlled trials of omalizumab (Niven 2008 and EXALT) were included in secondary analyses. Only the results using the double-blind studies and incorporating results for both mepolizumab 75mg and 100mg are presented here (see section 4.10).

Figure 3. Network meta-analysis diagram for clinically significant exacerbations (mepolizumab 100mg and 75mg, double blind trials) Figure 20 on page 139 of the company's submission



4.22 The company conducted the indirect treatment comparison using a Bayesian random-effects method and a fixed-effects method. The results from the company's base case network analysis are presented in table 6. The company acknowledges that the results should be treated with caution since only a small proportion of patients in the mepolizumab and omalizumab trials were eligible for both treatments, and study populations differed in terms of severity. However, the company states that in patients who are eligible for both drugs, mepolizumab would be at least as effective as omalizumab.

Table 6 Results of the company's network meta-analysis for mepolizumab compared with omalizumab (modified ITT overlap population, double blind

RCTs, mepolizumab 75mg and 100mg) Source: Table 44 on page 98 of the ERG report

Outcome	Model	Population 3 Mean / median risk ratio (MD) or rate ratio (RR) (95% credible interval)
Clinically significant exacerbations	Fixed effects	RR 0.664 (0.51 to 0.86)
	Random effects	RR 0.664 (0.28 to 1.50)
Exacerbations requiring hospitalisation	Fixed effects	RR 0.932 (0.35 to 2.49)
	Random effects	RR 0.937 (0.29 to 3.06)
Change from baseline in % predicted FEV_1	Fixed effects	MD 0.645 (-2.65 to 3.9)
	Random effects	MD 0.653 (-2.88 to 4.23)

ERG comments

4.23 The ERG stated that the methods of indirect comparison were appropriate. The ERG noted that there was heterogeneity in the trials including that the proportion of people with severe asthma differed between the mepolizumab and omalizumab trials, with a greater proportion of people with severe asthma in the mepolizumab trials. The ERG considered that this may lead to a biased estimate in favour of mepolizumab because a higher treatment effect would be expected in a more severe asthma population. The ERG also considered that given the concerns over heterogeneity between studies, a random effects model would be more appropriate for all scenarios and endpoints and the results of the fixed effects network meta-analysis should be interpreted with caution.

Adverse effects of treatment

4.24 The company presented adverse event data from DREAM, MENSA and SIRIUS. Based on a pooled analysis, the following adverse events were more than twice as frequent for mepolizumab compared with placebo: eczema (RR 5.34, 95% CI 1.25 to 22.78), nasal congestion (RR 2.62,

95% CI 0.89 to 7.72) and dyspnoea (RR 2.2, 95% CI 0.78 to 6.20). The incidence of drug-related adverse events was 16% in the placebo group compared with 23% in the mepolizumab 100 mg SC group and 18% in the mepolizumab 75 mg IV group. The most frequently reported drug-related adverse events in the placebo and mepolizumab 100 mg SC and 75 mg IV groups were headache (2%, 5%, and 3%, respectively) and injection site reaction (3%, 6%, and 2%, respectively).The company stated that safety profile is similar to standard of care, with the exception of an increased rate of injection site reactions with mepolizumab.

4.25 The company also presented data on adverse events for mepolizumab 100mg SC from the COSMOS and COLUMBA studies, both single arm open label extension studies for the MENSA and SIRIUS trials and the DREAM trial respectively. In both studies the most frequent adverse events were nasopharyngitis (30% COSMOS, 26% COLUMBA), upper respiratory tract infection (16% COSMOS, 13% COLUMBA), headache (14% COSMOS, 21% COLUMBA) and injection site reactions (4% COSMOS, 9% COLUMBA).

ERG comments

4.26 The ERG noted that mepolizumab appears to be generally well tolerated in severe eosinophilic asthma patients. However, there was only a small amount of long-term safety data available for mepolizumab. The ERG noted that 5%-6% of patients on 100mg mepolizumab developed anti-mepolizumab antibodies, but the company stated that this did not discernibly impact upon the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients.

5 Cost-effectiveness evidence

Model structure

5.1 The company submitted a de novo Markov model to assess the cost-effectiveness of mepolizumab compared with standard care and

compared with omalizumab. For the comparison with standard care, the company presented results for:

- the modified ITT population (defined by a blood eosinophil count of ≥150 cells/μL at initiation of treatment or ≥300 cells/μL in the prior 12 months; and ≥2 exacerbations in the previous year),
- the company's proposed population (blood eosinophil count of 150 cells/μl at initiation of treatment and 4 or more exacerbations in the previous year or were dependent on systemic corticosteroids; representing [redacted] of the MENSA population) and
- the company's proposed population excluding people on maintenance corticosteroids with <4 exacerbations.

For the comparison with omalizumab, the company presented results based on the modified ITT overlap population rather than in its proposed population because it did not have access to patient level data for omalizumab.

5.2 The mean age for patients in the model was 50.1 years. The model used a lifetime horizon, with a cycle length of 4 weeks. The company discounted costs and benefits at 3.5% per year and did not apply a half cycle correction. The company stated that costs were from the perspective of the NHS and Personal Social Services.

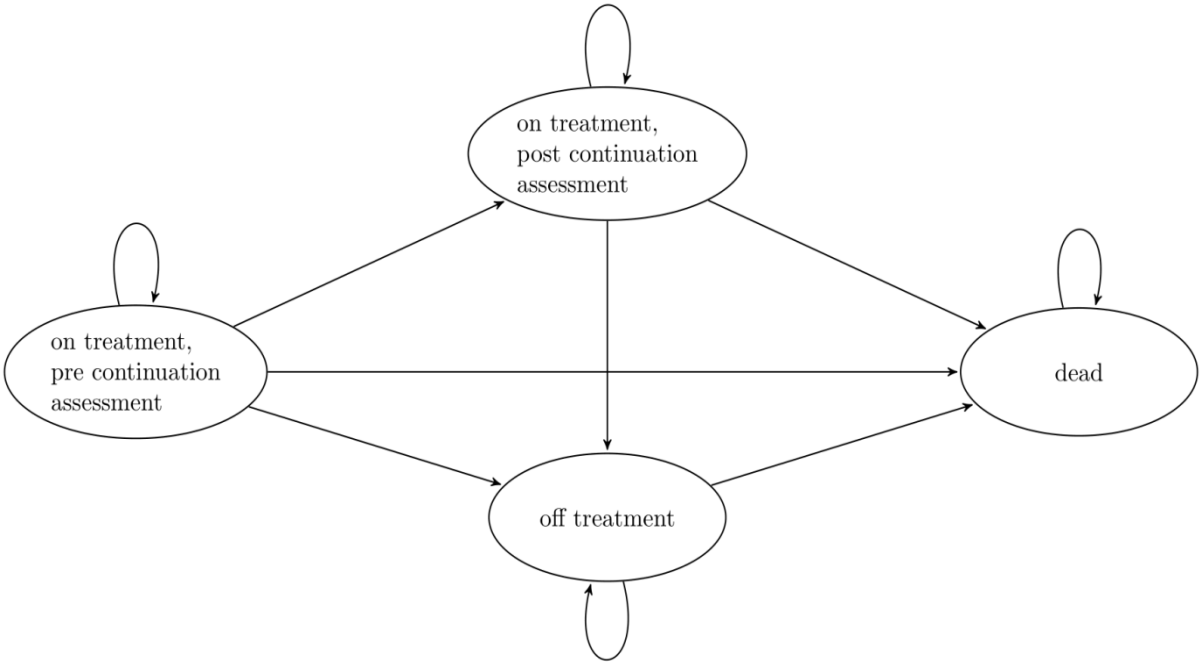
The model had 4 health states:
- off treatment,
- on treatment pre-continuation assessment,
- on treatment post-continuation assessment, and
- death.

People treated with mepolizumab or omalizumab entered the model in the health state 'on treatment pre-continuation assessment' and remained there until assessed at 12 months if taking mepolizumab or 16 weeks if taking omalizumab. Patients transitioned to the 'on treatment

post-continuation assessment' state if they met the criteria to continue treatment or otherwise to the 'off treatment' state. Patients in the 'off treatment' health state remain there until death, and the company assumed that patients treated with standard care start in this health state. Patients in the 'on treatment post-continuation assessment' state remain there until they stop treatment die. Treatment duration in the base case was assumed to be 10 years, with a yearly 10% attrition rate after 1 year. Of note, the company assumed that the treatment benefit observed with mepolizumab continues for the duration of the model. The company consider that exacerbations decrease utility, increase risk of death, increase costs, with a health state (rather than being separate health states per se). During each cycle patients may experience one of the three types of clinically significant exacerbations:

1. an exacerbation requiring treatment with oral corticosteroids
2. an exacerbation requiring an emergency department visit, or
3. an exacerbation requiring hospitalisation.

Figure 3 Model Structure (Source: Figure 10 on page 110 of the ERG report)



Model details

5.3 The company based the effectiveness of mepolizumab compared with standard care on the clinically significant exacerbation rates from the MENSA trial. Until patients are assessed at 12 months to decide if treatment should continue, the company assumed that people on mepolizumab experience the mean treatment effect for people randomised to mepolizumab in MENSA. Beyond this, the company used patient level data from MENSA at 32 weeks for patients who met the criteria to continue beyond 12 months. Patients who do not meet the criteria to continue get standard care and experience the exacerbation rates of the standard care group (see Table 7 below).

Table 7 Clinically significant exacerbation rates used in the company's model comparing mepolizumab with placebo (Source: Table 51 on page 111of the ERG report

Technology	Modified ITT 4 weekly rate	Company proposed population 4 weekly rate	Company proposed population excluding people on maintainance corticosteroids with < exacerbations 4 weekly rate
Standard care	0.134	0.239	0.204
Add-on mepolizumab (pre-continuation assessment)	0.067	0.093	0.093
Add-on mepolizumab (post-continuation assessment)	0.042	0.056	0.050

Data from MENSA tria l,mepolizumab 75mg IV or 100mg SC

5.4 For the comparison with omalizumab, the company obtained the effectiveness estimates for clinically significant exacerbation rates compared with standard care from the company's fixed effects network meta-analysis up until the point at which patients would be assessed for continuing (or not) (at 52 weeks for mepolizumab and at 16 weeks for omalizumab) and then applied the rates from the MENSA trial for mepolizumab and from INNOVATE for omalizumab.

Table 8 Clinically significant exacerbation rates for the ITT population used in the company's model comparing mepolizumab with standard care (Source: Table 53 and 54 in the ERG report)

	Rate ratio vs. Placebo	4-weekly rate

Add on mepolizumab pre-continuation assessment	0.496 (	0.066
Add on mepolizumab post-continuation assessment	0.316(	0.042
Add on omalizumab pre-continuation assessment	0.746	0.101
Add on omalizumab post continuation assessment	0.373	0.050

5.5 In the model, the company assumed that a patient could die from asthma only after a clinically significant exacerbation. In the base case analysis, the company chose mortality rates following exacerbations involving hospitalisation from a study in patients hospitalised for acute severe asthma by Watson et al., which it supplemented with relative rates of asthma-related mortality outside of hospital reported in a report by the National Review of Asthma Deaths . The company assumed in its model that patients may die of other causes and used age-dependent transition probabilities both for general mortality and asthma related mortality.

5.6 The company obtained utility values for mepolizumab by mapping St George's Respiratory Questionnaire scores (SGRQ) in the MENSA trial to EQ-5D. The mapping algorithm was based on a population with chronic obstructive pulmonary disease (not eosinophilic asthma). The company explored EQ-5D values directly from the DREAM trial in a scenario analyses. The company assumed that the utility estimates for omalizumab were the same as those of mepolizumab. The company looked to Lloyd et al for disutilities associated with exacerbations of 0.10 (requiring oral corticosteroids) and 0.20 (requiring hospitalisations). The company assumed that an exacerbation leading to an emergency department visit would have the same disutility as an exacerbation requiring oral corticosteroids (0.10). The company did not include

adverse reactions in the model because of the small differences between treatment groups.

Table 9 Utility estimates used in the model compared to directly measured EQ5D scores from the DREAM trial (Source: Table 56 on page 116 of the ERG report)

	ITT population Utility score (Standard error)		Company proposed population excluding people on maintainance corticosteroids with < exacerbations Utility score (Standard error)		Company proposed population Utility score (Standard error)	
	EQ-5D	SGRQ-mapped	EQ-5D	SGRQ-mapped	EQ-5D	SGRQ-mapped
Mepolizumab: pre-continuation assessment	0.802 (0.005)	0.796 (0.010)	0.829 (0.009)	0.793 (0.021)	0.827 (0.007)	0.777 (0.017)
Standard care	0.794 (0.005)	0.738 (0.015)	0.797 (0.011)	0.682 (0.038)	0.785 (0.009)	0.708 (0.029)
Mepolizumab: post-continuation assesment	0.824 (0.006)	0.806 (0.009)	0.834 (0.012)	0.805 (0.018)	0.837 (0.009)	0.795 (0.016)

5.7 The company included the following costs in its model: drug acquisition costs, administration costs, monitoring costs and costs associated with managing exacerbations. The cost of mepolizumab per 4-weekly cycle was assumed to be equal to the price of a 100mg mepolizumab vial, which is administered once every four weeks. The company included the price based on the confidential patient access scheme for mepolizumab in the model. The components of standard care the company based on MENSA and included in the model at list price. The company included the list price for omalizumab because it did not have access to the confidential patient access scheme (discount) price for omalizumab. whereas the ERG presented analyses comparing mepolizumab and

omalizumab based on their discounted prices. The exact dose of omalizumab depends on weight and IgE level and the company calculated this using 2 different approaches, one incorporating data measuring the dosing distribution of omalizumab in England (resulting in costs of £872.22 per cycle per person) and the other based on the NICE mutiple technology appraisal for omalizumab (resulting in costs of £617.99 per cycle per person). A detailed description of the costs in the model is presented on pages 210–16 of the company submission

ERG comments

5.8 The ERG stated that its clinical advisers considered that a lifetime duration of mepolizumab was more plausible, because there is no fixed treatment stopping rule in clinical practice. The ERG therefore considered that 10 year stopping rule in the model was inappropriate, and performed exploratory analyses (see section 5.22 and 5.23).

5.9 The ERG had concerns around the stopping rule in the model. The ERG stated that the company proposed continuing treatment unless a patient's rate of exacerbation increases. This would mean that a subgroup of patients remain on treatment even when not improving, which may not be aligned with clinical practice. The ERG requested that the company present exploratory analyses linking the continuation criteria with improvement in exacerbations. But, the company was not willing to quantify improvement in terms of fewer exacerbations because some patients on maintenance oral corticosteroids may not have fewer exacerbations but instead may take lower doses of corticosteroids. The ERG also noted that patients who do not continue mepolizumab experience the same rates of exacerbation as patients in the standard care group which the ERG believes would underestimate the exacerbation rate in this subgroup.

5.10 The ERG stated that the rates of exacerbation chosen by the company for patients who continue mepolizumab could be inappropriate. The ERG noted that these rates were measured in the MENSA trial shortly after

patients started treatment, and so might not reflect the long-term effectiveness of mepolizumab. In contrast, the COSMOS study measured rates of exacerbation for a full year in patients who had already been on mepolizumab for 32 weeks. This would also account for the seasonal nature of asthma exacerbations. The percentage of MENSA patients that went on to participate in COSMOS equals those meeting the continuation criteria in the modified ITT population of MENSA (90.1% vs 90.9%). The ERG requested that the company to present exploratory analyses using more plausible data from COSMOS. The company declined stating that the exacerbation rate in COSMOS in patients treated with mepolizumab during MENSA (0.9) was similar to that measured in the ITT population in MENSA (0.877). The ERG agreed, but noted that the exacerbation rates are different to the rate used in the model for patients on mepolizumab meeting the continuation criteria (0.55 in the ITT population). The ERG also considered that the SIRIUS study better estimated the rate of exacerbations in people treated with oral corticosteroids than the MENSA trial, as the specific population in the SIRIUS trial was people with severe eosinophilic asthma who required regular treatment with maintenance systemic corticosteroids and high-dose inhaled corticosteroids. The ERG performed exploratory analyses including the exacerbation rates from COSMOS and SIRIUS (see section 5.22 and 5.23).

5.11 The ERG stated that it would have been more appropriate for the company to model the directly-obtained EQ5D utility estimates from the DREAM trial, according to the NICE reference case. The ERG questioned mapping data from people with chronic obstructive pulmonary disease rather than asthma. The ERG also noted that the length of utility decrement from exacerbations was based on a study by Lloyd which assumed a four-week utility decrement. The ERG also noted that Lloyd did not report the disutility estimated for exacerbations requiring a visit to an emergency department. The ERG noted that using the average length of the exacerbations in MENSA instead of the length

of exacerbations based on Lloyd et al would have been more appropriate. The ERG presented exploratory results varying these assumptions (see section5.22 and 5.23.)

5.12 The ERG considered that the company should have used the mortality rate for asthma from the Roberts study rather than the Watson study. The ERG explained that the Watson study measured asthma-related mortality at ages 18 to 44 years and 45 years and over; therefore, the study assumed a constant rate of asthma-related mortality for people aged 45 years and over. The ERG considered that the Roberts study provided more accurate asthma mortality estimates because it stratified patients into narrower age bands. including for people aged 65 years and over. To cite, the ERG noted that the asthma-related mortality rate was approximately six times higher in the 65 years and over group than that in the 45-54 years age group in the Roberts study. The ERG considered that the Watson study overestimated mortality between the ages of 45 and 65 years and underestimated mortality in people 65 years and over. The ERG concluded that because the median age of the patients in the model was 50.1 years, and because the model treatment duration was 10 years, then the model likely overestimated the asthma - related mortality during the treatment period, thereby also overestimating the benefits of mepolizumab (see section 5.22 and 5.23).

Company's base-case results and sensitivity analysis

5.13 The base-case results for the company's comparison of mepolizumab with standard care are presented in table 10. For the company's proposed population, the incremental cost-effectiveness ratio (ICER) was £19,526 per quality adjusted life year (QALY) gained. The base-case results for the company's comparison of mepolizumab with omalizumab in the 'overlap population' are presented in table 11. These results have been calculated by the ERG using the company's assumptions while applying the confidential patient access schemes for both mepolizumab and omalizumab.

Table 10 Company's base case results for mepolizumab (using PAS price) compared with standard care (Source Table 60 on page 119 of the ERG report)

	ITT population			Company proposed population excluding people on maintainance corticosteroids with <4 exacerbations			Company proposed population		
	Mepo	SoC	Mepo vs. SoC	Mepo	SoC	Mepo vs. SoC	Mepo	SoC	Mepo vs. SoC
Deterministic results									
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			£31,659			£15,394			£19,526
Probabilistic results									
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			£31,692			£15,478			£19,511

- The intention-to-treat (ITT) population (all trial patients who were randomised and received at least one dose of study medication), the company proposed population (blood eosinophil count of 150 cells/µl at initiation of treatment and 4 or more exacerbations in the previous year or were dependent on systemic corticosteroids)

Table 11 Company's base case results for mepolizumab (PAS price) compared with omalizumab (PAS price), overlap ITT population (Calculated by the ERG; source ERG confidential appendix)

	Mepolizumab	Omalizumab	Mepolizumab vs. omalizumab	Standard care	Mepolizumab vs. SoC
Probabilistic results					
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			[redacted]		**£31,617**

5.14 The company's probabilistic analysis showed that if the maximum acceptable amount for an additional QALY was £30,000 then mepolizumab would have a 56% probability of being cost effective compared with standard care in the company's proposed population.

5.15 In response to a request from the ERG, the company provided separate results for people with a blood eosinophil count of ≥150 cells/μL when starting treatment, who were dependent on systemic corticosteroids yet who had fewer than 4 exacerbations per year. The company reported an ICER of £78,716 per QALY gained for mepolizumab compared with standard care. The increase in the ICER was because of: (i) a lower exacerbation rate; (ii) fewer exacerbations requiring hospitalisation (and so lower asthma related mortality), and; (iii) and a smaller difference in the utilities between mepolizumab and the comparator in this subgroup.

5.16 The company conducted a series of univariate sensitivity analyses (for further details, see table 172 on page 224 of the company's submission). For the comparison of mepolizumab compared with standard care, the utility estimate applied to the standard care arm was the key driver of the cost-effectiveness results. None of the changes to the model parameters resulted in a base-case ICER of over £25,000 per QALY gained. The key driver of the cost-effectiveness results when comparing mepolizumab with omalizumab was the proportion of patients on omalizumab who met the continuation (stopping) criteria.

5.17 The company conducted a series of scenario analyses (for further details, see table 147 on page 244 of the company submission). In the company's proposed population, comparing mepolizumab with standard care, the biggest drivers of results were reducing the age at baseline to 30 years, including a shorter time horizon, using utility values mapped from SIRIUS, and using the Roberts study as an alternative source of

asthma related mortality. Additionally, in the modified ITT population, incorporating utilities based on the EQ-5D data from the DREAM trial had a large impact on the ICER.

5.18 The company also conducted a scenario analysis taking into account the costs and consequences of long-term systemic corticosteroid usage. For this, the company estimated the dose-dependent risk of developing 6 adverse events associated with systemic corticosteroid therapy: myocardial infarction, glaucoma, diabetes mellitus, cataracts, osteoporosis, and peptic ulcer. The company implemented a dose-reduction approach where a proportion of patients are assumed to stop oral corticosteroid maintenance treatment at a certain time point .The rate of oral corticosteroid sparing was based on the median oral corticosteroid dose reduction with mepolizumab treatment in SIRIUS at 24 weeks. The company did the analysis in the SIRIUS modified ITT population in which 24% of people in both treatment groups were assumed to be on maintenance oral corticosteroids at baseline, based on the results of the MENSA trial. In SIRIUS, at 24 weeks, patients in the mepolizumab group had reduced their daily maintenance oral corticosteroids by a median of 30%. The company also presented an alternative approach assuming that 6.9% of people treated with mepolizumab compared with standard care stopped maintenance oral corticosteroid treatment at 24 weeks (based on the results of the SIRIUS trial). Results based on both approaches had a negligible impact on the ICERs. (See Tables 154 and 155 on page 255 of the company's submission).

ERG comments

5.19 The ERG considered that the results of the company's oral corticosteroid sparing analyses should be treated with caution. The ERG noted that the company used data from MENSA to calculate exacerbation rates in mepolizumab patients yet used the corticosteoid usage reduction data from a different trial, SIRIUS. The ERG stated that this overestimated the

benefits of mepolizumab, because exacerbation rates might not decrease as much when reducing corticosteroid usage. The ERG noted the company used a 10 year time horizon instead of a lifetime. The ERG noted that this would underestimate the benefits of oral corticosteroid sparing because of the chronicity of the adverse effects associated with corticosteroids.

5.20 The ERG also noted that the company used data related to oral corticosteroid sparing from the modified ITT population of SIRIUS instead of the company's proposed population. The ERG noted that the company did not consider utility decrement from osteoporotic fractures; and considered only as a 'one off' some utility decrements from chronic conditions. The ERG noted that data relating to the proportion of patients who discontinue oral corticosteroids differ in this appraisal and in TA278: 14.5% of patients discontinued oral corticosteroids treatment in SIRIUS compared with 41.9% of omalizumab responders. In general, the ERG agreed with the company that the current analyses did not capture the impact on the ICER of reducing oral corticosteroids use.

ERG exploratory analyses

Mepolizumab compared with standard care

5.21 The ERG undertook a series of exploratory analysis using the company's economic model. The ERG had concerns about the company's proposed population being defined according to blood eosinophil count. The ERG stated that a population not restricted by blood eosinophil count, but who had 4 or more exacerbations, would have been more appropriate. However, the ERG was unable to conduct this analysis because it did not have the data.

5.22 The ERG amended the company's model, which increased the company's base case ICER for mepolizumab compared with standard care in all populations. These are presented in table 12 below (See Table 70 in the ERG report for further details).

Table 12 Results of the scenario analyses performed by the ERG for mepolizumab compared with standard care (using mepolizumab PAS price)

	ITT population	Company's proposed population	Company proposed population excluding people on maintainance corticosteroids with <4 exacerbations
Company base case	£31,692	£19,511	£15,478
EQ-5D utilities (DREAM)	£40,932	£20,863	£18,429
Asthma mortality Roberts/Watson	£42,728	£27,544	£20,735
Lifetime on biologics	£32,130	£19,763	£15,571
Exacerbation utility decrement - MENSA	£32,480	£19,963	£15,690
Exacerbations rates for patients meeting continuation criteria from COSMOS	£37,190	£22,239	£17,240
ERG base case (combining all 5 amendments	£72,596	£35,440	£33,520

above)			

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Mepolizumab compared with omalizumab

5.23 For the comparison of mepolizumab with omalizumab in the population eligible for both, based on the modified ITT population, and using PAS prices for both technologies, the ERG made the following amendments to the company's model. The ERG made the 5 amendments listed in section 5.22 and this resulted in omalizumab being dominated by mepolizumab and ICER of £73,537 per QALY gained compared with standard care. Additionally the ERG carried out the following scenario analyses:

- Estimating the cost of omalizumab as per the omalizumab MTA (using PAS prices)
- Using the exacerbation rates ratios based on people on maintenance oral corticosteroids from the SIRIUS study
- Using the results of the network meta-analysis random effects model

Combining all the ERG's exploratory analyses reversed the results and mepolizumab was dominated by omalizumab. The ICER for mepolizumab compared with standard care increased to £105,455 per QALY gained in this 'overlap' population.

Innovation

5.24 The company stated that mepolizumab is innovative because it provided a step change in the treatment of severe asthma, was first in its class, had a novel mechanism of action and does not require dose calculation based on body weight or blood eosinophil level.

6 Equality issues

6.1 No equalities issues were raised during the NICE scoping process. The company raised a potential equity issue if people on maintenance corticosteroids who have <4 exacerbations in the previous year are excluded from a positive recommendation, because this group represents a more severe population and is likely to benefit from a reductions in corticosteroid exposure.

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Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003860/human_med_001933.jsp&mid=WC0b01ac058001d124

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003860/WC500198037.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Mepolizumab for treating severe eosinophilic asthma [ID798]

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of mepolizumab within its marketing authorisation for treating severe eosinophilic asthma

Background

Asthma is a chronic inflammatory disease associated with variable airflow obstruction and airway hyperresponsiveness. It is characterised by exacerbations associated with symptoms such as breathlessness, chest tightness, wheezing, sputum production and cough. Severe eosinophilic asthma is a subset of the condition that is associated with blood and sputum eosinophils and recurrent exacerbations. Eosinophilic nasal polyps may also be present. Eosinophils are thought to play a major role in airway inflammation in asthma.

People with severe asthma often have a severely impaired quality of life which can lead to fatigue, absence from school or work and psychological problems including stress, anxiety and depression. There were 1242 deaths from asthma in the UK in 2012. Estimates suggest that around 5.4 million people in England and Wales currently receive treatment for asthma.

Current British guidelines from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) recommend a stepwise approach to treatment in adults. Control is maintained by stepping up treatment as necessary and stepping down when control is good. The guideline steps are summarised as follows:

- Step 1. Inhaled short-acting beta-2 agonist as required.
- Step 2. Add inhaled corticosteroid (200–800 micrograms per day).
- Step 3. Add an inhaled long-acting beta-2 agonist. If control remains inadequate, increase the dose of the inhaled corticosteroid to 800 micrograms per day. If there is no response to the inhaled long-acting beta-2 agonist, stop this drug and increasing the inhaled corticosteroid dose 800 micrograms per day. If control is still inadequate, try a leukotriene receptor antagonist or slow-release theophylline.
- Step 4: Consider increasing the dose of inhaled corticosteroid up to 2000 micrograms per day. Consider adding a fourth drug (for example, a

leukotriene receptor antagonist, slow-release theophylline or a beta-2 agonist tablet).

- Step 5: Use daily steroid tablets at the lowest dose providing adequate control. Maintain high-dose inhaled corticosteroid at 2000 micrograms per day. Consider other treatments to minimise the use of steroid tablets. Refer patients to specialist care.

NICE technology appraisal guidance 278 recommends omalizumab as an option for treating severe persistent allergic IgE-mediated asthma as add-on therapy to optimised standard therapy in people aged 6 years and older who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year), and only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme. Optimised standard therapy is defined in the recommendations as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta2 agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.

The technology

Mepolizumab (Nucala, GlaxoSmithKline) is an anti-interleukin-5 humanised monoclonal antibody. By reducing the effects of interleukin-5, mepolizumab causes a reduction in circulating eosinophils, a type of white blood cell involved in allergic response and tissue inflammation. Mepolizumab is administered subcutaneously in addition to best standard asthma care.

Mepolizumab does not currently have a marketing authorisation in the UK for treating severe eosinophilic asthma. Mepolizumab has been studied in clinical trials in comparison with placebo in people with severe eosinophilic asthma.

Intervention(s)	Mepolizumab (in addition to best standard care)
Population(s)	Adults with severe eosinophilic asthma
Comparators	• Best standard care without mepolizumab For people with severe persistent allergic IgE-mediated eosinophilic asthma: • Omalizumab

Outcomes	The outcome measures to be considered include: • asthma control • incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation • use of oral corticosteroids • patient and clinician evaluation of response • lung function • mortality • time to discontinuation • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.

Other considerations	Best standard care for this population is considered to be step 4 and/or step 5 in the stepwise approach to treatment from the SIGN/BTS guideline. If the evidence allows, social factors affecting adherence to treatment will be considered. If the evidence allows, the following subgroups will be considered: • People who do not adhere to treatment • People who have severe allergic IgE-mediated eosinophilic asthma • People who require maintenance oral corticosteroid treatment • People who require frequent oral corticosteroid treatment. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 278, Apr 2013, 'Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201)'. Review proposal date Mar 2016. Technology Appraisal No. 138, March 2008, 'Inhaled corticosteroids for the treatment of chronic asthma in adults and in children aged 12 years and over'. Guidance on static list. Related Guidelines: Clinical Guideline in Preparation, 'Asthma – diagnosis and monitoring'. Anticipated publication date: TBC Clinical Guideline in Preparation, 'Asthma management'. Earliest anticipated publication date: June 2017. Related Interventional Procedures: Interventional Procedure No. 419, Jan 2012, 'Bronchial thermoplasty for severe asthma'. Related Quality Standards:

	Quality Standard No. 25, Feb 2013, 'Asthma'. Related NICE Pathways: NICE Pathway: Asthma, Pathway created: Mar 2014.
Related National Policy	NHS England (January 2014) Adult Highly specialised respiratory services. Manual for prescribed specialised services 2013/14. NHS England (2014) Internal Medicine's Group: A14. Specialised Respiratory. Department of Health (2013) NHS Outcomes Framework 2014-2015

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Single Technology Appraisal (STA)

Mepolizumab for treating severe eosinophilic asthma [ID798]

Final matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • GlaxoSmithKline (mepolizumab) Patient/carer groups • Action Against Allergy • Allergy UK • Anaphylaxis Campaign • Asthma UK • British Lung Foundation • European Federation of Allergy and Airway Diseases Patients Association (EFA) • South Asian Health Foundation • Specialised Healthcare Alliance Professional groups • Association of Respiratory Nurse Specialists • British Geriatrics Society • British Society for Allergy & Clinical Immunology • British Thoracic Society • Primary Care Respiratory Society UK • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal Pharmaceutical Society • Royal Society of Medicine • UK Clinical Pharmacy Association Others • Department of Health	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies • Novartis Relevant research groups • Asthma, Allergy and Inflammation Research Trust • British Association for Lung Research • Cochrane Airways Group • MRC Clinical Trials Unit • National Institute for Health Research • National Society for Research into Allergy Evidence Review Group • BMJ Group • National Institute for Health Research

Appendix C

Consultees	**Commentators (no right to submit or appeal)**
• NHS England • NHS Newbury and District CCG • NHS Sheffield CCG • Welsh Government	Health Technology Assessment Programme <u>Associated Guideline groups</u> • National Clinical Guideline Centre <u>Associated Public Health groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Organisations that accept an invitation to participate in the appraisal; the company that manufactures the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: manufacturers of comparator technologies; Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Mepolizumab for treating severe refractory eosinophilic asthma in adults [ID798]

Company evidence submission

20th November 2015

File name	Version	Contains confidential information	Date
[ID798]-mepolizumab-company submission-20112015 [ACIC]	1.0	Yes	20/11/2015

Contents

Tables and figures

1 Executive summary

Mepolizumab
Mepolizumab (brand name Nucala®) is a humanised anti-IL5 monoclonal antibody (IgG1, kappa); a first in class biologic targeted therapy for severe refractory eosinophilic asthma (Section 2.1). Mepolizumab binds with high specificity and affinity to human interleukin-5 (IL-5) which prevents binding to the receptor complex expressed on the eosinophil cell surface. This inhibits IL-5 signaling and the over expression of peripheral blood and tissue eosinophils. Eosinophilic inflammation of the airways plays a central role in the pathogenesis of asthma (Section 2.1.1).

Mepolizumab has received positive CHMP opinion for the treatment of severe refractory eosinophilic asthma in adults (Section 2.2). A licence for this indication is expected at the end of November 2015. Mepolizumab is intended as a long term treatment added on to Standard of Care (SoC) and is administered as a 100mg fixed-dose 4-weekly subcutaneous injection. The draft SmPC recommends that the need for continued therapy should be considered at least on an annual basis (Section 2.3).

Aligned with the current practice in England and Wales for severe asthma, the key comparator for add-on mepolizumab is SoC (consisting of high dose inhaled corticosteroids [ICS] and additional maintenance treatment[s] including maintenance oral corticosteroids (mOCS)) (Section 3.3). A small proportion of mepolizumab eligible patients (estimated [redacted]) would alternatively be eligible for treatment with omalizumab (an anti-IgE biologic therapy that is the subject of NICE guidance, TA278). Omalizumab is therefore considered as a secondary comparator in this submission (Section 3.3).

Severe refractory eosinophilic asthma
Severe refractory asthma describes the 5-10% people with asthma who despite attempts to control their disease following the step-wise treatment recommendations suffer from frequent exacerbations and limited control of symptoms (Section 3.1). Patients experience compromised quality of life from both their asthma and as a result of treatment-related side effects. The National Report for Asthma Deaths (NRAD) concluded that of the 155 deaths for which severity could be estimated, 39% had severe asthma in the 12 months prior to death (Section 3.5).

People with severe refractory asthma are typically termed Step 4 or Step 5 patients in the British Thoracic Society / Scottish Intercollegiate Network Guidelines (BTS/SIGN) for asthma management. Beyond high dose ICS plus additional maintenance treatment[s] and short courses of oral corticosteroids (Step 4) there are limited therapeutic options available although a small proportion of severe refractory asthma patients are eligible for omalizumab (Section 3.3).

Beyond this the only alternative treatment option is maintenance oral corticosteroids (mOCS). For patients at Step 5 who may well have gained control with mOCS, the primary objective is to minimise exposure to OCS but maintain asthma control. The need to protect patients from active doses of systemic steroids due to their established short- and long-term adverse event profile is a broad-based public health goal.

Target population for this submission
The licensed indication (draft) of mepolizumab is for the treatment of severe refractory eosinophilic asthma in adults. However, mindful of NHS resources and with the objective of focussing the submission on a population more likely to provide a cost effective use of NHS resources, we have identified a sub-group of this patient population with an enhanced capacity to benefit from treatment (section 4.7). A post-hoc analysis identified a blood eosinophil count of ≥150 cells/μL at initiation as predictive of response to mepolizumab. Further to this, predictive modelling showed that patients with a higher historic exacerbation rate (≥4 in the previous 12 months) experienced a greater numerical reduction in exacerbations per annum than those with fewer exacerbations (<4). Clinical experts agree that this population is plausible and practical to implement in practice. We seek guidance in the following population:

GSK proposed population

Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or dependency on systemic corticosteroids (mOCS).

The extent of the incremental benefit vs. SoC on improvement of asthma control for those patients receiving mOCS may be reduced; for these patients the primary objective is to reduce steroid exposure whilst maintaining asthma control. However, steroid sparing benefits are not fully captured in the clinical and cost effectiveness analysis. While, exclusion of systemic steroid users who do not fulfil the ≥4 exacerbation in the previous year criterion results in additional clinical and cost-effectiveness benefit, we believe it would be unethical and clinically unsound to exclude the more severe mOCS users from guidance. To ensure a balanced evaluation of the proposed population including and excluding mOCS users with < 4 exacerbations we will present the results for (Section 4.7):

- **GSK proposed population** (≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or dependency on mOCS with < 4 exacerbations in past year)
- **GSK proposed population excluding mOCS users with <4 exacerbations** (≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year excluding mOCS users with <4 exacerbations in the previous year)

Clinical effectiveness of mepolizumab
The efficacy of add-on mepolizumab compared to SoC alone has been demonstrated in one phase IIb double-blinded randomised controlled trial (RCT), a 52 week dose ranging study (DREAM, N=616) and more relevant for this submission two Phase III double-blinded RCT studies; MENSA a 32 week exacerbation reduction study (N=576) and SIRIUS a 24 week OCS sparing study (N=135) (section 4). Below are results for the GSK proposed population in the licensed dose and posology (100mg SC) of add-on mepolizumab therapy compared to SoC alone in the following Phase III studies:

MENSA exacerbation reduction study

MENSA demonstrated that mepolizumab reduced clinically significant exacerbations, improved the health-related quality of life (HRQL) and asthma control compared to SoC alone in the GSK proposed population and GSK proposed population excluding mOCS users with < 4 exacerbations.

- A statistically and clinically significant 50% reduction (p=0.002) in the rate of clinically significant exacerbations over SoC alone was observed in the GSK proposed population. A 61% reduction (p<0.001) was observed in the GSK proposed population excluding mOCS users with <4 exacerbations.
- A 51% reduction (p=0.157) in exacerbations requiring hospitalisation /emergency department visits in the GSK proposed population. A 55% reduction (p=0.177) was observed in the GSK proposed population excluding mOCS users with <4 exacerbations.
- A 45% reduction (p=0.372) in hospitalisation in the GSK proposed population compared to a 51% reduction (p=0.338) in the GSK proposed population excluding mOCS users with <4 exacerbations.
- A statistically and clinically significant improvement in quality of life (SGRQ, MCID ≥4) of -10 units (p<0.001) in the GSK proposed population was observed. This was -12.8 units (p<0.001) in the GSK proposed population excluding mOCS users with <4 exacerbations.
- A statistically and clinically significant improvement was also observed for asthma control (ACQ, MCID ≥0.5) in the GSK proposed population of -0.79 units (p<0.001) compared with -0.96 units (p<0.001) in the GSK proposed population excluding mOCS users with <4 exacerbations.

SIRIUS OCS sparing study
SIRIUS demonstrated that mepolizumab reduced mOCS dose whilst maintaining asthma control compared to SoC alone. As all patients in the study were on mOCS (including patients with more and less than 4 exacerbations in the past year), only the 150cells/μL at initiation of treatment criterion had to be applied to select the GSK proposed population from the ITT population. As there were reduced patient numbers in this subgroup there was inadequate powering for statistical analysis, and therefore the results are supportive of the ITT population where statistically significant improvements are observed.

- A 1.81 odds of achieving a reduction in OCS dose versus SoC (p=0.115).
- A 50% reduction in OCS dose or to a dose ≤ 5mg is achieved in approximately 50% of patients (48% vs. 38% and 50% vs. 40% [100mg SC vs. SoC], respectively).
- A clinically meaningful improvement in ACQ (-0.65 unit difference to SoC alone, p=0.002) and quality of life (SGRQ, -5.6 unit difference to SoC alone, p=0.066).

COSMOS – Open label extension to MENSA and SIRIUS
Many MENSA and SIRIUS patients continued into the now concluded open label extension (OLE) study, COSMOS. In the ITT population, COSMOS has demonstrated the effectiveness of mepolizumab for an additional 52 weeks in:

- Maintaining exacerbation reductions at 0.93/year
- Maintaining asthma control (ACQ -0.09 from baseline)

- Maintaining a continued OCS dose of 2.5mg/day throughout the additional 52 weeks.

The clinical effectiveness of add-on mepolizumab compared with add-on omalizumab is derived indirectly through a network meta-analysis. Without individual patient level data for omalizumab the comparison could not be made in the GSK proposed population and the NICE recommended population for omalizumab. In a comparison of the ITT population, (pooling MENSA 75mg IV and 100mg SC mepolizumab data) the treatment effect based on a reduction of clinically significant exacerbations was RR 0.664 (95% CrI 0.513-0.860) with a 99% probability of favouring mepolizumab. Although this result should be interpreted in the context of limited available evidence to inform the analysis it is not unreasonable to conclude that mepolizumab is likely to be at least as effective as omalizumab in the overlap population.

Safety of mepolizumab
Overall mepolizumab was well tolerated when administered at 100mg SC in 4-weekly intervals (section 4.12). The majority of adverse events were mild, with the most commonly reported adverse drug reactions being headache and nasopharyngitis. Injection site reactions were more frequent in patient administered mepolizumab (8%) vs. SoC alone (3%). All patients were monitored for an hour post administration of mepolizumab in the clinical trial program and there were no cases of anaphylaxis. Neutralising antibodies were detected in one subject. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients.

Cost-effectiveness
A de novo 5 state Markov model was developed in Microsoft Excel® which projected the expected clinical and economic outcomes for severe refractory eosinophilic asthma patients (section 5.2-5.5). A life time horizon was modelled (in 4-weekly cycles) and biologic treatment was assumed to be maintained for responding patients for up to 10 years. For comparison of add-on mepolizumab versus SoC alone the risk of exacerbation, day-to-day symptoms (SQRQ-derived EQ-5D values), frequency and resource for exacerbation resolution were taken from MENSA. Asthma related mortality assumptions were taken from the literature. The main submission reports the cost effectiveness of add-on mepolizumab (inclusive of a proposed PAS to the DH) versus SoC alone and versus omalizumab (list price).

In the GSK proposed population excluding mOCS users with <4 exacerbations the ICER of add-on mepolizumab compared with SoC alone is £15,478 / QALY gained and this rises to £19,511 / QALY gained in the GSK proposed population (see Table 2 and Section 5.8). The worsening of the ICER by including patients on mOCS (with a lower exacerbation history in the previous 12 months) reflects the level of asthma control of these patients as a result of being on OCS and therefore the reduced incremental benefit of introducing mepolizumab. However, it should be noted that these patients are still in need of an OCS sparing alternative treatment to minimise exposure and associated short and long-term side effects.

Univariate sensitivity analyses identified a number of sensitive parameters however the resultant ICER remained below £25,000 / QALY gained in the GSK proposed

population. The scenario analyses (see Section 5.8.3) showed that the ICER was sensitive to the starting age of the patient cohort; a reflection of the associated reduced mortality for a younger cohort, the time horizon of the model where the true long term benefits of mepolizumab could not be captured and asthma-related mortality. The evidence to support the risk of asthma-related mortality in this severe population is limited and subject to assumptions. Indeed this remained a key issue in the recent NICE MTA of omalizumab (TA278). Dependent on the source of mortality and its application in the model, the resultant ICER in the GSK proposed population ranged from £15,645 / QALY gained (in a like-NICE approach) to £29,833 /QALY gained conservatively applying the risk of mortality to only those patients experiencing an exacerbation requiring a hospitalisation. The true ICER is likely to reside somewhere between this range of values however would still provide a cost effective use of NHS resources.

Compared to list price add-on omalizumab the ICER is dominant with mepolizumab offering QALY gains and cost savings (see Table 2). The QALY gain needs to be interpreted with caution given the limitations of the evidence to inform the network meta-analysis.

Table 1 Summary of the cost-effectiveness results for add-on mepolizumab (net price) versus SoC alone in people with severe refractory eosinophilic asthma

	Total costs		Total QALYs		∆ Costs	∆ QALYs	ICER
	Mepo	SoC	Mepo	SoC	Vs. SoC	Vs. SoC	
GSK proposed population excluding mOCS users with <4 exacerbations in the previous year							
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]			
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£15,478**
L 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
U 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
GSK proposed population							
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]			
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£19,511**
L 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
U 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Table 2 Summary of the cost-effectiveness results for add-on mepolizumab (net price) versus add-on omalizumab (list price) alone in people with severe refractory eosinophilic asthma

	Total costs		Total QALYs		∆ Costs	∆ QALYs	ICER
	Mepo	Oma	Mepo	Oma	Vs. Oma	Vs. Oma	
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]			
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
L 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
U 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Confidential addendum

The ERG and Committee are asked to refer to a confidential addendum for the cost-effectiveness analyses of mepolizumab (+PAS) versus omalizumab (GSK estimated PAS)

Budget impact

Based on GSK's proposed population it is estimated that there are 16,166 patients eligible for treatment with add-on mepolizumab. Over the next 1-5 years it is

expected that approximately 2,318 patients across NHS England and Wales will commence treatment with add-on mepolizumab.

Summary

For people with severe refractory eosinophilic asthma there are limited therapeutic options. These patients remain at risk of exacerbations, their quality of life is negatively impacted and they place a significant burden on the NHS. Given the long-term health consequences of mOCS, which are difficult to capture fully in the economic evaluation, there is a clear need for a targeted therapy to enable the severe asthma patients to be managed with a reduced level of steroid exposure. For those patients with a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or dependency on systemic corticosteroids (mOCS) mepolizumab provides a cost effective alternative to both SoC and omalizumab. Mepolizumab fits well within the current treatment services for severe asthma and through fixed dosing of 100mg 4-weekly subcutaneous injection provides assurance of a predictable budget impact.

1.1 Statement of decision problem

The Decision Problem addressed in this submission is summarised in Table 3.

Table 3 The decision problem addressed by this submission

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with severe eosinophilic asthma	Evidence is presented for the anticipated licensed population for mepolizumab. We demonstrate the clinical and cost-effectiveness of mepolizumab in a more severe patient population. We seek guidance in the following population: *Adults with severe refractory eosinophilic asthma with a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or dependency on mOCS.*	Mindful of NHS resources and current NHS implementation of NICE guidance for another biologic in severe asthma (omalizumab) guidance is sought in a more severe sub-population of the anticipated licensed indication. This sub-group provides enhanced clinical benefit whilst maintaining a cost-effective proposition for the NHS.
Intervention	Mepolizumab (in addition to best standard care)	Consistent with Final Scope	N/A
Comparator (s)	• Best standard care without mepolizumab For people with severe persistent allergic IgE-mediated eosinophilic asthma: • Omalizumab	Consistent with Final Scope	N/A
Outcomes	The outcome measures to be considered include: • asthma control • incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation • use of OCS • patient and clinician evaluation of response • lung function • mortality • time to discontinuation • adverse effects of treatment • health-related quality of life.	Consistent with Final Scope. • asthma control (Section 4.7) • incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation (Section 4.7) • use of OCS (Section 4.7) • patient and clinician evaluation of response (Section 4.7 and Appendix 8.6) • lung function(Section 4.7) • mortality (Section 4.12, 4.13 and 5.3.6) • time to discontinuation (withdrawals are described Section 4.5 and 4.12) • adverse effects of treatment(Section 4.12) • health-related quality of life (Section 4.7)	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be	Consistent with the Final Scope. • A PAS has been submitted to DH/PASLU (see	N/A

	expressed in terms of incremental cost per quality-adjusted life year (QALY), the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	Section 2). • Costs are considered from an NHS perspective. • A PSS perspective is considered in the narrative.	
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • People who do not adhere to treatment • People who have severe allergic IgE-mediated eosinophilic asthma • People who require maintenance oral corticosteroid treatment • People who require frequent oral corticosteroid treatment.	Where evidence is available this has been presented within the submission document. • People who do not adhere to treatment (patients were required to be adherent to optimised SoC in order to be eligible for mepolizumab) • People who have severe allergic IgE-mediated eosinophilic asthma (Section 4.10) • People who require maintenance oral corticosteroid treatment (Section 4.7 and 5.7) • People who require frequent oral corticosteroid treatment (Section 4.7 and 5.7)	N/A
Special considerations including issues related to equity or equality		Consistent with Final Scope. • No equality issues have been identified. • A possible equity issue has been identified (Section 3.7).	• The primary treatment objective for uncontrolled patients at Step 4 who have not commenced on mOCS is to achieve a reduction in exacerbations. This is also true for those patients uncontrolled at Step 5 on mOCS. • For patients at Step 5 who are controlled on mOCS, not only is the treatment objective be reduce the exacerbation frequency, (although the potential to do so may be less than patients at Step 4 due to the impact of the mOCS) clinicians will also be seeking to reduce the systemic exposure to OCS while maintaining asthma control. It is unlikely that we can appropriately capture, economically, the true long term benefit of reducing an individual's systemic exposure to OCS. • This is important to note to ensure that any guidance fairly reflects all needs of the patient population in question, which may not be able to be fully captured in the presented economic evaluation.

2 The technology

2.1 Description of the technology

The following technology is under assessment:

Generic name: Mepolizumab
Brand name: Nucala®
Approved name: Nucala 100 mg powder for solution for subcutaneous injection

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa), directed against human interleukin 5 (IL-5) produced in Chinese hamster ovary cells by recombinant DNA technology.

2.1.1 Mechanism of action

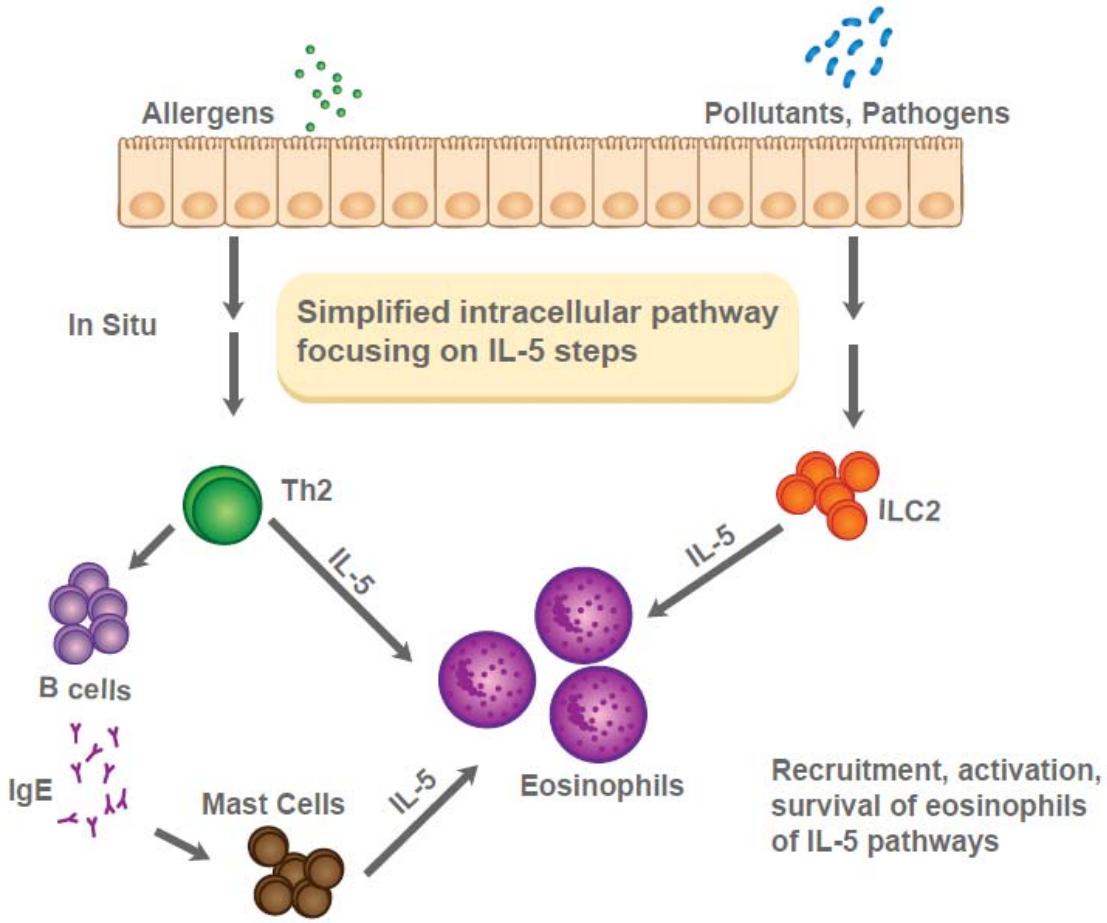
Eosinophilic inflammation of the airways plays a central role in the pathogenesis of asthma with the frequency of asthma exacerbations appearing to be closely related to airway inflammation.[1-5] Eosinophilic inflammation is promoted by T-helper 2 (Th2) and type 2 innate lymphoid cells (ILC2s) associated with cytokines (Figure 1).[6]

Mepolizumab binds with high specificity and affinity to human interleukin 5 (IL-5), the key Th2 cytokine responsible for the regulation of blood and tissue eosinophils. Mepolizumab prevents IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits IL-5 signaling and the over expression of peripheral blood and tissue eosinophils. The overproduction of IL-5 has been specifically reported in patients with a variety of eosinophil associated disorders including asthma.[7,8] Th2-driven disease promotes tissue eosinophilia and therefore lung damage;[9] and biopsy and sputum studies have shown that eosinophils are key drivers of uncontrolled disease.[10,11] Good correlations have been shown between elevated sputum eosinophil levels and blood eosinophil counts[12].

By neutralising IL-5 and reducing eosinophilic inflammation in the lung, mepolizumab reduces exacerbations, improves asthma control and reduces OCS dependency while maintaining asthma control. Since mepolizumab binds only to IL-5, it is not expected to elicit unintended biological consequences which can result from off-target or non-specific binding. Available data do not indicate that reduction of eosinophils has any untoward effects on normal health.[13]

Thus, a strategy targeting IL-5 with mepolizumab represents a first in class targeted therapeutic option for patients with eosinophilic inflammation associated with severe asthma despite receiving optimised SoC therapy.

Figure 1 Pathways leading to eosinophilic inflammation (adapted from Mukherjee et al. 2014[14] and Brusselle et al. 2013[3]



2.2 Marketing authorisation/CE marking and health technology assessment

The marketing authorisation application for mepolizumab for adult severe refractory eosinophilic asthma was submitted to the European Medicines Agency (EMA) on 3rd November 2014. It is currently under review via the centralised procedure. Positive Committee for Medicinal Products for Human Use (CHMP) opinion was received on 24th September 2015. The EU Commission Decision was positively received on the 2nd December 2015.

2.2.1 Anticipated Indication

The anticipated indication is as follows:

Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adult patients

2.2.2 Expected contraindications

Contraindications are expected to include hypersensitivity to the active substance or any excipients listed in the draft SmPC (see reference pack).[15]

2.2.3 Regulatory considerations

During the regulatory process there was extended discussion on the specificity of the indication statement with regards to identifying an eosinophil threshold that predicts response to add-on mepolizumab. The summary EPAR is provided in the reference pack. The final EPAR is expected to be available within 15 days of the Commission Decision which will be sent to NICE once available. It is anticipated that there will be no special conditions attached to the marketing authorisation.

2.2.4 Date of availability

It is anticipated that mepolizumab will be made commercially available in 1Q 2016.

2.2.5 Regulatory approval beyond the UK

Regulatory approval was granted in the US by the FDA on 4th November 2015. Mepolizumab is indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

2.2.6 Other UK Health Technology Assessment (HTA)

GSK expects to make a submission to the Scottish Medicines Consortium (SMC) at the end of 4Q 2015 with advice expected 2Q 2016.

2.3 Administration and costs of the technology

A summary of mepolizumab unit cost, dose and method of administration is provided in Table 4.

Table 4 Summary of the technology: Mepolizumab (draft SmPC)[15]

Pharmaceutical formulation	Powder solution for injection (Lyophilised white powder)
Acquisition cost (excluding VAT)	List price: £840 per 100mg vial PAS net price: [redacted] per 100mg vial The patient access scheme has been submitted to the Department of Health / PASLU and is currently being evaluated. It is a straight discount that will be applied at the point of invoice.
Method of administration	For subcutaneous (SC) injection only. Mepolizumab should be administered by a healthcare professional as a SC injection into the upper arm, thigh, or abdomen. It should be reconstituted prior to administration and should be used immediately upon withdrawal from the vial into a syringe. Note that Chemical and physical stability of the reconstituted product have been demonstrated for 8 hours when stored below 30°C.
Doses and frequency	Adults aged 18 and over: 100mg administered subcutaneously once every 4 weeks.
Average length of a course of treatment	Mepolizumab is intended for long-term treatment. The need for continued therapy should be considered on at least an annual basis as determined by a physician assessment on the patient's disease severity and level of control of exacerbations.

	In practice, patients on mepolizumab may be assessed at more regular intervals in line with local treatment protocols.
Average cost of a course of treatment	Cost of a year of treatment every 4 weeks (excluding administration costs): List price: £840 x 13 administrations = £10,920 PAS net price: [redacted] x 13 administrations = [redacted] (Please also refer to confidential addendum)
Dose adjustments	Mepolizumab has fixed dose administration with no dose adjustment required for weight. No dose adjustment is required for elderly patients, hepatic impaired or renal impaired (with creatinine clearance values between 50-80 mL/min). There are limited data available in patients with creatinine clearance values <50 mL/min.
Anticipated care setting	In England this will be given as part of a severe asthma clinic, which may be in a specialist tertiary care centre, while in Wales this is more likely to be in a secondary care setting.

2.4 Changes in service provision and management

No additional tests or investigations are necessary to identify the population for whom mepolizumab is indicated in the marketing authorisation. Severe asthma patients are already phenotyped in a specialist setting. A blood test for eosinophil levels is required to identify those patients that are likely to experience a clinically significant response to mepolizumab and this already forms part of the routine assessment of patients during screening for severe asthma.

Mepolizumab will be administered in a specialist setting most likely by a specialist respiratory nurse. Mepolizumab requires reconstitution with 1.2mL of sterile water, typically complete within approximately 5 minutes.[15] Appropriate facilities already exist for the administration of omalizumab (a biologic for severe allergic, IgE driven asthma; see section 3.3). However, increased capacity as a result of increasing demand from patients deemed eligible for mepolizumab may need to be addressed.

Monitoring requirements for mepolizumab directly following administration will be driven by locally led protocols. Although there is no formal requirement in the draft SmPC, in mepolizumab clinical trial protocols, patients were monitored for one hour following administration.[16] Monitoring protocols post-administration of omalizumab already exist although increased capacity to meet the demand from mepolizumab patients again may need to be addressed. There are no concomitant therapies specified in the draft SmPC; mepolizumab is an add-on therapy to optimised SoC consisting of high dose ICS and additional maintenance treatment[s].

Mepolizumab will fit into the already existing A14 Service Specification for Severe Asthma in England,[17] which already includes biologic administration. It is expected that severe asthma services will remain centrally commissioned under NHS England at the time of launch.

2.5 Innovation

Mepolizumab is an innovative step change in the treatment of severe asthma. It provides the first biologic therapy for severe asthma in over 10 years and more

importantly has a novel mechanism of action in binding to IL-5. Mepolizumab is anticipated to be the first licensed add-on treatment to standard of care for severe refractory eosinophilic asthma patients. Add-on mepolizumab does not require a dose calculation based on weight or eosinophil level, and is administered as a fixed 100mg SC dose 4 weekly. This should provide the NHS with surety of budget impact unlike omalizumab.

In the absence of mepolizumab, there are limited therapeutic options for patients with persistently poor asthma control who are ineligible for omalizumab other than oral corticosteroids (OCS). Patients with severe asthma are at high risk of exacerbations, which impacts quality of life and places a significant burden on the NHS.[18-21] BTS/SIGN guidelines recommend the use of OCS at the lowest possible dose for severe asthma patients that are uncontrolled at Step 4[22] and cautions that patients on long term steroid tablets or those requiring frequent courses of steroids will be at risk of systemic side effects (see Section 3.3). Add-on omalizumab, an anti IgE biologic therapy for severe persistent allergic asthma is considered a steroid sparing alternative for some patients (BTS/SIGN guidelines), however recent evidence suggests that the overlap population that are eligible for both mepolizumab and omalizumab is limited ([redacted])[23] and there remain a significant number of patients for which mepolizumab remains the only treatment option beyond mOCS (see Section 3.3).

Mepolizumab has demonstrated a reduction in clinically significant exacerbations, and improvement in health-related quality of life and a reduction in long term exposure to OCS whilst maintaining asthma control across the phase IIb/III clinical trial program. The long term costs and consequences of patients on maintenance OCS are considered as part of a scenario analysis in the economic evaluation. The full extent of these side effects represents a substantial impact for both patients and the NHS beyond that which can be captured in QALY calculations. In the cost effectiveness analysis the cost/QALY is largely driven by the day to day quality of life and impact on exacerbations rather than the steroid sparing effect which has proven more difficult to capture and quantify. For those patients that are on maintenance OCS, where the treatment objective may be to reduce the OCS burden whilst maintaining asthma control the difference in quality of life for those on add-on mepolizumab compared to SoC is smaller than those not on maintenance OCS who may be exacerbating more frequently. This suggests that the health related quality of life instruments are not sensitive enough to capture the longer term consequences of exposure of OCS, and captures only the short term benefit of achieving better asthma control. While there is limited data specific to the use of OCS in asthma, side effects of OCS use include fracture, osteoporosis, psychiatric conditions, sleep disturbance, skin thinning, hyperglycaemia and/or diabetes, weight gain, ocular conditions including cataracts, myocardial infarction, Cushinoid features, infections, ulcer, oedema, lipodystrophy, hypertension, muscle weakness, and adrenal insufficiency.[24-26] Asthma-specific quality of life scales may provide an overly positive estimation for patients frequently exposed to OCS and underestimate the benefit of steroid sparring interventions.[27]

In a publication by Asthma UK ‘Fighting for Breath’ (2010) the negative impact on quality of life as a result of steroids further described in terms of both the physical symptoms and how OCS make patients feel.[28] Furthermore a negative impact on

quality of life caused by steroid usage may be associated with non-adherence to steroids which consequently puts patients at risk of an exacerbation.[29] UK patients identified the fear of side effects as a reason for non-adherence, particularly psychological disturbances including anxiety, depression and steroid induced psychosis. [30] According to one patient, *"I didn't realise until I started taking them just the effect they could have on you mentally...."* .[30] Another stated, *"It's got to the point where I am on so much medication, sometimes I give up, and yes, because of the steroids, it causes depression..."* .[28] This impact in terms of patient quality of life cannot be fully captured in QALY calculations.

The QALY calculation will also not capture the negative HRQL of carers of patients with severe asthma of whom many report they do not get the same level of recognition compared with carers of other conditions.[28] Furthermore the QALY calculation does not take into consideration the extent of day to day symptoms which can make it difficult for some patients to maintain previous full time employment and unlike other chronic conditions it can be more challenging for severe asthma patients to obtain a disability allowance.[28] With the introduction of add-on mepolizumab, the resultant reduction in exacerbations and reduction in exposure and resultant long term consequences of OCS means that patients (and their carers) may experience an improvement in their quality of life and additionally for some may enable them to return to work.

Mepolizumab is highly innovative with the potential to provide a step change in the management of their condition. In particular for those patients for whom the primary treatment objective is to reduce dependence on oral corticosteroids whilst maintaining asthma control the impact on health related benefits are unlikely to be fully reflected in the QALY calculations included in this submission.

2.6 External advice

Reference is made throughout the submission to two advisory boards where advice was sought on the way in which severe asthma is currently treated, the applicability of the mepolizumab clinical data to UK practice and on the clinical assumptions underpinning the economic evaluation (Section 5.3). The first advisory board took place on 19 March 2015 in London and was attended by four Respiratory Consultants treating severe asthma patients and three Health Economists/National level Payers. The second advisory board took place on 23 July 2015 in Motherwell and was attended by 4 Respiratory Consultants treating severe asthma patients in Scotland and 3 Health Economists / National-level Payers. The questions for which advice was sought are provided in Appendix 8.1.

3 Health condition and position of the technology in the treatment pathway

3.1 Severe asthma

Asthma is a chronic heterogeneous lung disease characterised by inflammation, narrowing of the airways, and reversible airway obstruction. The majority of patients with asthma can be adequately controlled by following step-wise treatment recommendations as stated in the British Thoracic Society/Scottish Intercollegiate Guideline Network - Management of Asthma.[22] However, a minority of patients (approximately 5%) experience uncontrolled asthma despite attempts to control their disease.[28] A Task Force, supported by the European Respiratory Society (ERS) and American Thoracic Society (ATS) recently stated that when a diagnosis of asthma is confirmed and co-morbidities have been addressed, severe asthma is defined as ''asthma that requires treatment with high dose inhaled corticosteroids [ICS] plus a second controller and/or systemic corticosteroids to prevent it from becoming 'uncontrolled' or that remains 'uncontrolled'[1] despite this therapy.[20] The uncontrolled subjects of the above definition are classified as refractory.

This group of high-risk patients may suffer from frequent exacerbations, limited control of symptoms, and compromised quality of life from both their asthma and as a result of treatment-related side effects.[20] Exacerbations are particularly disabling for patients and typically require treatment with systemic corticosteroids and may require hospital admission. Despite current treatments asthma patients are at increased risk of death. One of the strongest predictors of death due to asthma is asthma-related hospitalisation (including hospitalisation as a result of an exacerbation).[31,32] This links with the fact that patients with severe asthma are also the heaviest users of health services, and around 80% of asthma spend is used on the 20% with the severest symptoms.[33]

3.2 Severe refractory eosinophilic asthma

Evidence shows that once a correct diagnosis of asthma has been made, co-morbidities addressed and therapy 'optimised', patients with severe asthma are comprised of complex, overlapping and non-overlapping phenotypes and one example of such is the severe eosinophilic asthma phenotype.[20] Studies in the severe asthma population have shown that more than half of these patients have persistent eosinophilic airway inflammation despite high dose inhaled corticosteroid therapy.[34,35] Eosinophilic asthma can be associated with increased asthma severity, late-onset disease, and a refractory response to even high doses of inhaled corticosteroids requiring treatment with parenteral or oral steroids).[18,19] Eosinophilic asthma inflammation can be measured in both blood and sputum, but recent studies have confirmed that late-onset severe refractory eosinophilic asthma can be reliably

[1] Chung 2014: Uncontrolled asthma defined as at least one of the following: 1) Poor symptom control: ACQ consistently .1.5, ACT ,20 (or ''not well controlled'' by NAEPP/GINA guidelines) 2) Frequent severe exacerbations: two or more bursts of systemic CS (.3 days each) in the previous year 3) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year 4) Airflow limitation: after appropriate bronchodilator withhold FEV1 ,80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal). Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics).

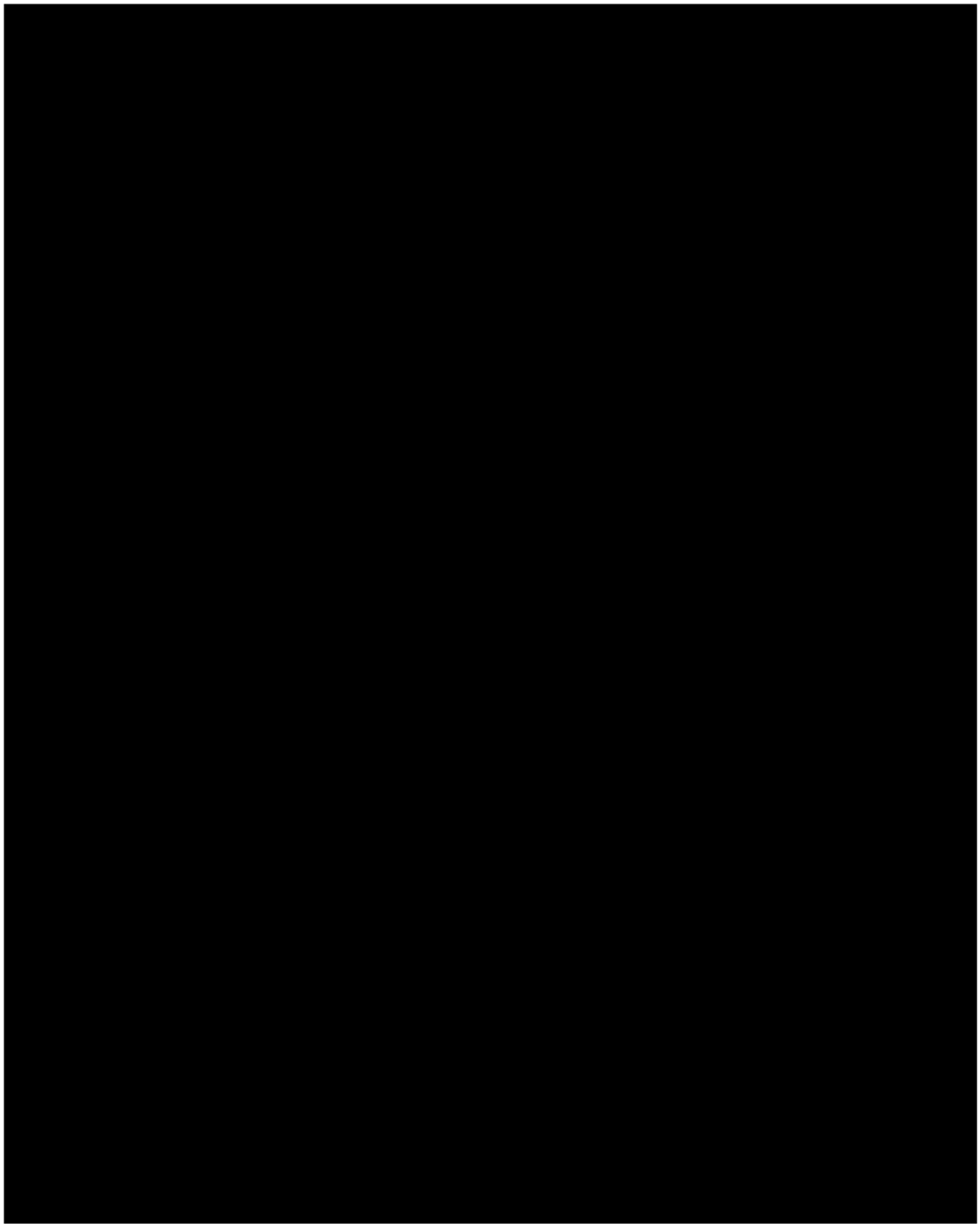
characterised by establishing blood eosinophil thresholds in the presence of high-dose ICS in a poorly controlled exacerbating phenotype.[36,37]

3.3 Clinical care pathways

In accordance with the BTS/SIGN Guideline and as recommended by the ATS/ERS Task Force gaining control for severe asthma patients should first be attempted through the use of high-dose ICS and other controllers, such as long-acting β-agonists, leukotriene antagonists or theophyllines.[22,20] Only then should daily OCS be considered and at the lowest possible dose to achieve adequate control (see Figure 2). We refer to this treatment regime in this submission as standard of care (SoC) which is identified as the key comparator for add-on mepolizumab. The BTS/SIGN guideline refers to other available treatments and steroid sparing treatments. Other available treatments include immunosuppressants such as methotrexate[38,39], cyclosporine[40,41], and oral gold[42] which have demonstrated variable and marginal effects on OCS reduction but with significant toxicity. BTS/SIGN only recommend the above immunosuppressants as a three months trial, and only if other drug treatments have been proven unsuccessful.[22] Bronchial thermoplasty is also considered a treatment option for adult patients who have poorly controlled asthma despite optimal therapy. However, the BTS/SIGN Asthma guidelines suggests this results in a modest improvement in asthma quality of life in the year after treatment[22] and produces no consistent improvement in asthma symptoms or FEV_1.[43-45] None of these treatment options were identified as relevant comparators for this appraisal.

The BTS/SIGN Guideline also refers to omalizumab (Xolair, a humanised monoclonal antibody which binds to circulating IgE, reducing levels of free serum IgE) which targets a different pathway to mepolizumab, as a steroid sparing agent for patients at Step 5. This is consistent with the NICE pathway for asthma.[46] In 2013 NICE completed a multiple technology appraisal (MTA, TA 278) for omalizumab and recommended it as a treatment option for treating severe persistent confirmed atopic IgE-mediated asthma as an add-on to optimised standard therapy in patients ≥6 years, who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year) (along with an approved confidential patient access scheme). However, only a small proportion of patients with severe asthma and an allergic phenotype are appropriate candidates for its use based on specific weight, IgE levels and a positive test for a perennial allergen. Add-on omalizumab is identified as an additional comparator for add-on mepolizumab however this is only appropriate for the overlap population of patients exhibiting both an allergic (atopic) and eosinophilic asthma phenotypes (see Figure 2). It is estimated, from a non-drug interventional study that the GSK proposed population represents approximately [redacted] of the severe asthma adult population in England and Wales. Of those patients eligible for mepolizumab, an estimated [redacted] are also eligible for add-on omalizumab.

Figure 2 BTS/SIGN Guidelines with positioning of biologics (adapted from BTS/SIGN Guidelines [47])



3.4 Effects of the disease / condition on patients, carers and society

According to the Asthma UK report *Fighting for Breath*, severe asthma means different things to different patients (i.e. it is not only heterogeneous in its clinical features but also its impact on patients' lives). Some people live with daily symptoms of breathlessness whilst others have sudden severe asthma attacks with little warning. Patients, therefore, adapt to cope with the impact of the disease on their lives.[28] The extent of day to day symptoms can make it difficult for some patients to maintain previous full time employment and unlike other chronic conditions it can be more challenging for severe asthma patients to obtain a disability allowance.[28] Resultant financial stress can further negatively impact a patient's HRQL. Asthma UK reports that the impact of caring for someone with severe asthma is substantial, impacting on family relationships and also difficulty in maintaining employment.[28]

Currently, patients with severe asthma who are at high risk of exacerbations and who are not eligible for omalizumab have few treatment options available other than OCS. Use of OCS on a regular basis has well-documented side effects. For these reasons, physicians and patients are reluctant to use OCS on a regular basis to control their asthma and even short-term to treat exacerbations. Consequently, it is not surprising that adherence to daily OCS has been documented to be as low as 50% or even less.[29,48]

Asthma exacerbations lead to over 50,000 hospital admissions per annum and total asthma therapeutic spend in the UK is around £800 million annually.[17] In addition, it is estimated that asthma leads to a direct cost to the NHS of £1 billion and an indirect cost to society, due to time off work and loss of productivity, of £6 billion.[17]

3.5 Mortality

The National Report for Asthma Deaths (NRAD),[49] the most comprehensive and detailed review in to asthma deaths reported that of the 155 patients who died and for whom severity could be estimated, 61 (39%) appeared to have severe asthma in the 12 months prior to death. In this report severe asthma was defined as those who were prescribed four asthma medications and those who had been admitted to hospital in the past year, needed OCS daily or had two or more prescriptions for systemic corticosteroids in the past year. An estimated 5%[20] of asthma patients have severe asthma and therefore the study would suggest that risk of mortality is still an issue in this population.

3.6 Current severe asthma service provision

Patients with suspected severe asthma receive a multidisciplinary assessment and one example of such an assessment is that outlined in the NHS England A14 Service Specification for Severe Asthma.[17] This assessment seeks to explore co-morbidities and compliance prior to the initiation of treatment (which would include biologics). In England this usually takes place at a tertiary care centre or in Wales in specialist secondary care clinics. We believe mepolizumab will fit into the existing care pathway for severe asthma.

3.7 Equality and Equity

The NICE scoping process did not identify any issues of equality or equity. However at the Decision Problem meeting GSK highlighted the possible risk of Committee issuing guidance which may not be deemed equitable across the eligible patient population. The primary treatment objective for severe refractory eosinophilic asthma patients uncontrolled at Step 4 who have not commenced on maintenance OCS is to achieve a reduction in exacerbations. This is also true for those patients uncontrolled at Step 5 on maintenance OCS. For those patients at Step 5 who are controlled on maintenance OCS, not only will the treatment objective be to reduce the exacerbation frequency, clinicians will also be seeking to reduce the systemic exposure to OCS while maintaining asthma control. For the GSK proposed population it is likely that we have not been able to appropriately capture, economically, the true long term benefit of reducing an individual's systemic exposure to OCS as the model primarily focuses on asthma control. Therefore this population will appear less cost-effective compared to the GSK proposed population when excluding mOCS users who did not achieve the required 4 exacerbations in the previous year, despite representing a more severe population. Thus, to ensure this equitability issue is addressed both populations (GSK proposed population and GSK proposed population excluding mOCS users with < 4 exacerbation in the previous year) are presented in the clinical and cost effectiveness section (section 4 and 5, respectively).

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

A systematic review was carried out to identify, report and if appropriate meta-analyse or indirectly compare any clinical studies of relevance to this appraisal. The review was conducted and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The primary objective of the systematic review was to evaluate the efficacy, health related quality of life (HRQL) and safety of mepolizumab relative to other maintenance treatments for severe asthma. Only data in relation to interventions identified in the Decision Problem (see section 1 and section 3.3): mepolizumab, SoC and omalizumab, are presented in the main body of the submission. *Note that the systematic review conducted, had a broader remit than this appraisal. It is available as a reference to this submission*.[50]

4.1.1 Search strategy

A comprehensive search strategy was designed to retrieve relevant clinical data from the published literature; details can be found in Appendix 8.2. The search strategy was split into two parts:

- Search strategy A: Tailored to identify relevant RCTs for maintenance treatment of severe asthma.
- Search strategy B: Focused on identifying efficacy/safety observational studies for omalizumab, and maintenance OCS.

Table 5 outlines the search engines and electronic databases that were searched. The search PICOS is described in Table 6. All databases were searched without limits with the exception of conference abstracts which were searched from 2012-2014 (2015 conference abstracts were not yet available). It was assumed that abstracts older than three years were likely to have been published as full text articles. All searches were executed on 16th July 2015 (an update to original searches conducted on 8 July 2014).

Table 5 Search engines and databases searched

Search engine (website)	Databases	Limits
ProQuest (www.proquest.com/)	• Medline® • EMBASE® • MEDLINE® In-Process • PASCAL	**Search Strategy A:** No limits **Search Strategy B:** 2004-2014
Cochrane (www.cochrane.org/)	• Cochrane - systematic reviews (CDSR) • Database of Abstracts of Reviews of Effects (DARE) • Cochrane - central register of controlled trials (CENTRAL) • Health Technology Assessments Database (HTA)	**Search Strategy A:** No limits **Search Strategy B:** 2004-2014
National Institute for Health Research	• Evidence Review Group (ERG) reports • Manufacturers submissions	**Search Strategy A & B** No limits

(NIHR) (http://www.hta.ac.uk/erg/index.asp)		
Conference abstracts (websites in next column)	• American Thoracic Society (ATS) • European Respiratory Society (ERS) • American College of Chest Physicians (ACCP)	**Search Strategy A & B:** Time limit (years): 2012 – 2014 (2015 conference abstracts not yet available)
Clinical trial registries (websites in next column)	• National Institutes for Health (NIH) ClinicalTrials.gov Register • Australian New Zealand Clinical Trials Registry (ANZCTR) • Registro Brasileiro de Ensaios Clinicos (ReBec)	**Search Strategy A & B** No limits
HTA organisations	**Search Strategy B only** • NICE single technology appraisals (STA) and multi technology appraisals (MTA)/guidelines • German Federal Joint Committee (G-BA) reports • Institute for Quality and Efficiency in Health Care (IQWiQ) reports • Pharmaceutical Benefits Advisory Committee (PBAC) reports • Haute Autorité de Santé (HAS) reports • National Commission for Incorporation of Technologies (CONITEC) • The Canadian Agency for Drugs and Technologies in Health (CADTH)	**Search strategy B** No limits
Regulatory drug agencies	**Search Strategy B only** • US Food and Drug Administration (FDA) reports • European Medicines Agency (EMA) reports • Brazilian Health Surveillance Agency (ANVISA)	**Search strategy B** No limits

4.1.2 Study selection

Once the searches were performed, eligibility of articles was assessed by two independent researches, based on the pre-specified PICOS and inclusion and exclusion criteria (see Table 6 and refer to the systematic review report). Selection was firstly based on title and abstract but where inclusion still remained unclear full texts were evaluated. The comparators for this appraisal are SoC and omalizumab however the initial search was broad and the review included other targeted and non-targeted agents used in the treatment of severe asthma.

Table 6 PICOS and eligibility criteria applied to the search strategies.

Topic	Inclusion criteria	Rationale	Exclusion criteria
Population	• Asthma patients with the following characteristics: o Patients age >12 years) o Severe (or refractory / difficult-to-treat / persistent / treatment-resistant / uncontrolled) asthma	• Mensa study population included patients ≥12 years. The review was conducted before submission of the regulatory application – where the licence is now expected in patients ≥18 years.	• Non humans • Healthy subjects • Other (respiratory) diseases besides asthma • Patients age ≤12 years) • Mild/moderate asthma*

	• Patients with and without eosinophilic and allergic asthma subtypes were included.	• To ensure totality of the available evidence could be considered.	• Studies including severe asthma patients, but not reporting results for this (sub) population.
Intervention	*Relevant to this appraisal*** • Active arm, Standard of Care with: o Mepolizumab o Omalizumab	• Identified by NICE scoping and concurred by clinical opinion gathered from advisory boards in March and August 2015.	• Studies not investigating one of the following treatments in the active arm: o Mepolizumab o Omalizumab o Standard of care • Studies investigating the impact of acute OCS treatment.
Comparators	• As above • *Note that the systematic review had a broader remit and included more comparators not deemed relevant for this appraisal; refer to full report for more details.*	• Selected to potentially enable both direct and indirect comparisons between the interventions of interest.	• Studies not investigating placebo, SoC or relevant active comparator in the comparator arm
Outcomes	• Efficacy (exacerbations, lung function, asthma control, symptoms, hospitalisations) • Steroid sparing • Rescue medication use (OCS/ICS) • HRQL (utilities) • Safety and tolerability *Note that additional Search Strategy B included adherence to treatment.*	• These outcomes were chosen since they are frequently measured and reported in trials of asthma/severe asthma. • Identified in the NICE Decision Problem (Section 1) and concurred with clinical opinion (from advisory boards conducted in March and August 2015, see section 2.6).	• Publications without at least one of the relevant endpoints.
Study design	**Search strategy A** • Double-blind, single-blind and open-label RCTs*** reporting efficacy and/or safety results (without restriction to date or language or study duration) • Systematic reviews including references to relevant RCTs**	**Search strategy A** • RCTs are the gold standard of clinical evidence, minimising the risk of confounding and allowing the comparison of the relative efficacy of interventions.	**Search strategy A** • Non-randomised clinical trials, case reports • Systematic reviews discussing only other trial designs besides RCTs or not discussing relevant outcomes • Posters which report no new/different study outcomes than the full publication reporting on the same trial.

	Search Strategy B • Observational studies • Systematic reviews including references to relevant observational studies**	**Search strategy B** • Provide longer-term real world effectiveness and supplement the evidence provided by RCTs.	**Search strategy B** • All other study types which are not observational. • Posters which report no new/different study outcomes than the full publication reporting on the same trial.
Language	• Publications in all languages were included	• To ensure where possible the totality of the evidence is not compromised.	• Not applicable
Timeframe	• Conference proceedings from the last three years (2012 – 2014 (2015 conference abstracts were not available, at the time of searching)) • No time limit was applied to all other publications and reports	• Assumed that conference proceeding older than three years were likely to have been published as full text articles.	• Conference proceedings older than three years (<2012)

* Studies with mild and/or moderate asthma patients were excluded in this review. Studies with moderate/severe asthma patients were included, if the majority of the patients had severe asthma (see protocol deviations below and in the full systematic review report).
*Other comparators included in the systematic literature review, but not reported in this submission include: reslizumab, benralizumab, tralokinumab, lebrikizumab, dupilumab and tiotropium.
*** RCT data were only extracted from publications which report primary results. Systematic reviews were screened for references to relevant RCTs, but data was not extracted from this source.

4.1.3 Protocol deviation

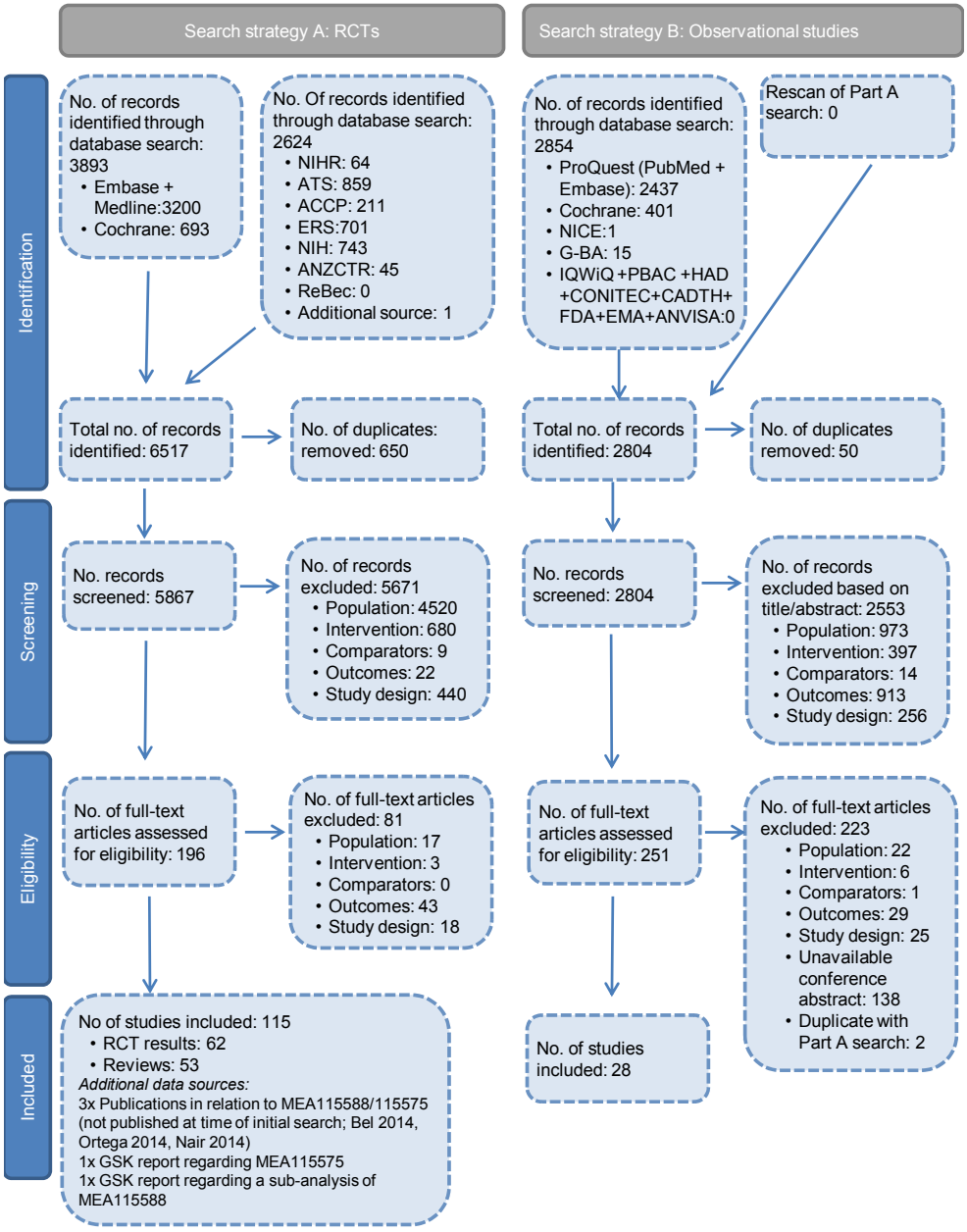
Two protocol deviations occurred with regards the inclusion and exclusion criteria to search strategy A (RCT search).

- Inclusion criteria of patients ≥12 years – one study was included with patients aged ≥ 11 years
- Studies including severe asthma patients but not reporting results for this sub population: When results were only reported for the total study population (moderate and severe), studies were included when the majority (≥50%) of patients had severe asthma.

4.1.4 Flow diagram of the included and excluded studies

Studies were included and excluded based on the criteria outlined in Table 6 and the results of each stage of the review process are outlined in Figure 3.

Figure 3 Flow diagram of included and excluded studies



GSK provided five additional data sources (hand searching) to the agency conducting the review which are highlighted in Figure 3 as 'Additional data sources'. GSK was aware of their relevance and that due to publication timing were unlikely to be identified through database literature or abstract searches (e.g. clinical study reports) Of the 62 RCTs and 5 additional data sources, 37 were deemed relevant to this appraisal. The remaining studies were not included since they do not address interventions of interest. A summary of the excluded RCTs is provided in appendix 8.2 and a reason for their exclusion. Search strategy B identified 28 relevant observational publications. A list of the included RCTs and observational studies are provided in Table 7 and Table 8 respectively.

Table 7 List of included RCTs

	Author, year	Type of document	Intervention	Comparator	Population
1	Pavord, 2012[36]	Full Text	Mepolizumab	Placebo	Severe eosinophilic asthma
2	Dotter, 2014[51]	Study report	Mepolizumab	Placebo	Severe refractory eosinophilic asthma
3	Haldar, 2009[52]	Full Text	Mepolizumab	Placebo	Refractory eosinophilic asthma
4	Nair, 2009[53,54]	Full Text	Mepolizumab	Placebo	Asthma who required treatment with oral prednisone to control symptoms and still had persistent sputum eosinophilia
5	Bel, 2014[55]	Full Text	Mepolizumab	Placebo	Severe eosinophilic asthma
6	Bel, 2015[56]	Abstract	Mepolizumab	Placebo	Severe eosinophilic asthma
7	Ortega, 2014[16]	Full Text	Mepolizumab	Placebo	Severe eosinophilic asthma
8	Nair, 2014[53]	Editorial	Mepolizumab	Placebo	Severe eosinophilic asthma
9	Holgate, 2004[57]	Full Text	Omalizumab	Placebo	Severe asthma
10	Humbert, 2005[58]	Full Text	Omalizumab	Placebo	Severe persistent asthma
11	Sthoeger, 2007[59]	Full Text	Omalizumab	Placebo	Severe persistent asthma
12	Humbert, 2008[60]	Full Text	Omalizumab	Placebo	Severe persistent allergic asthma
13	Hanania, 2011[61]	Full Text	Omalizumab	Placebo	Severe allergic asthma
14	Hanania, 2013[62]	Full Text	Omalizumab	Placebo	Allergic asthma
15	Bardelas, 2012[63]	Full Text	Omalizumab	Placebo	Inadequately controlled persistent allergic asthma
16	Busse, 2001[64]	Full Text	Omalizumab	Placebo	Severe allergic asthma
17	Finn, 2003[65]	Full Text	Omalizumab	Placebo	Severe allergic asthma
18	Lanier, 2003[66]	Full Text	Omalizumab	Placebo	Severe allergic asthma
19	Garcia, 2013[67]	Full Text	Omalizumab	Placebo	Severe, persistent, non-atopic asthma that was uncontrolled
20	Zakaria, 2013[68]	Abstract	Omalizumab	Placebo	Severe persistent asthma
21	Chanez, 2010[69]	Full Text	Omalizumab	Placebo	Severe persistent allergic asthma
22	Massanari, 2010[70]	Full Text	Omalizumab	Placebo	at least moderate persistent allergic asthma inadequately controlled
23	Ohta, 2009[71]	Full Text	Omalizumab	Placebo	Moderate-to-severe persistent asthma
24	Ayres, 2004[72]	Full Text	Omalizumab	Placebo	persistent moderate-to-severe allergic asthma
25	Niven, 2008[73]	Full Text	Omalizumab	Placebo	Inadequately controlled severe persistent allergic (IgE-mediated) asthma who were receiving high-dose ICS (>1000 mg/day

	Author, year	Type of document	Intervention	Comparator	Population
					beclometasone equivalent) plus a LABA.
26	Bousquet, 2011[74]	Full Text	Omalizumab	Placebo	Severe persistent allergic (IgE-mediated) asthma
27	Siergiejko, 2011[75]	Full Text	Omalizumab	Placebo	Severe persistent allergic (IgE-mediated) asthma
28	Hoshino, 2012[76]	Full Text	Omalizumab	Placebo	Severe allergic asthma
29	Rubin, 2012[77]	Full Text	Omalizumab	Placebo	Severe persistent asthma uncontrolled despite treatment
30	Solèr, 2001[78]	Full Text	Omalizumab	Placebo	Allergic asthma
31	Buhl, 2002[79]	Full Text	Omalizumab	Placebo	Allergic asthma
32	Buhl, 2002[80]	Full Text	Omalizumab	Placebo	Moderate-to-severe allergic asthma
33	Milgrom, 1999[81]	Full Text	Omalizumab	Placebo	Moderate to severe perennial allergic asthma
34	NCT00670930[82]	Clinical trials.gov	Omalizumab	Placebo	Moderate-Severe, Persistent Allergic Asthma
35	Bousquet, 2004[83]	Full Text	Omalizumab	Placebo	Allergic asthma, symptomatic despite moderate-to-high daily doses of ICS
36	Busse, 2013[84]	Letter to editor	Omalizumab	Placebo	moderate-to-severe allergic asthma who remain inadequately controlled on inhaled corticosteroids
37	Vignola, 2004[85]	Full Text	Omalizumab	Placebo	moderate-to-severe allergic asthma and moderate-to-severe persistent allergic rhinitis

Grey highlighted studies were not identified through the literature review but added to the data-extraction as 'hand searching, provided by GSK.

Table 8 List of included observational studies (studied omalizumab)

	Study	N	Follow-up duration	Design
1	Velling 2011[86]	13	52 weeks	Prospective monocenter investigation (one group)
2	Vennera 2012[87]	266	116.13 weeks	Post-marketing prospective observational surveillance trial (one group)
3	Rottem 2012[88]	33	52 weeks	Retrospective study (one group)
4	Korn 2010[89]	174	32 weeks	Retrospective study based on data from 2 post-marketing surveillance trials (one group)
5	Korn 2009[90]	280	26 weeks	Prospective study (one group)
6	Llano 2013[91]	266	116.13 weeks	Prospective study (one group)
7	Chivato 2009[92]	214	16 weeks	Retrospective study (one group)
8	Braunstahl 2013[93]	943	104 weeks	Prospective study (one group)
9	Van Nooten 2013[94]	154	52 weeks	Prospective study (one group)
10	Braunstahl 2013[95]	943	104 weeks	Prospective study (one group)

11	Grimaldi-Bensouda 2013[96]	767	87 weeks	Prospective study (two groups)
12	Tajiri 2014[97]	31	48 weeks	Prospective study (one group)
13	Molimard 2010[98]	166	Non-specific (beyond 16 weeks from initiation of omalizumab)	Retrospective study (one group)
14	Lafeuille 2012[99]	644	52 weeks	Retrospective study (one group)
15	Barnes 2013[100]	136	52 weeks	Retrospective study (one group)
16	Costello 2011[101]	93	26 weeks	Retrospective study (one group)
17	Zietkowski 2011[102]	19	16 weeks	Prospective study (two groups)
18	Brusselle 2009[103]	158	52 weeks	Prospective study (one group)
19	Kulichenko 2009[104]	15	52 weeks	n.a. (one group)
20	Lafeuille 2013[105]	3044	104 weeks	Retrospective study (four groups)
21	Kupyrs-Lipinska 2014[106]	11	n.a.	n.a. (one group)
22	Lafeuille 2012[99]	644	52 weeks	Retrospective study (one group)
23	Kuo 2014[107]	20	104 weeks	Retrospective observational registry study (eXpeRience study: Taiwan analysis; one group)
24	Pereira 2015[108]	62	104 weeks	Retrospective observational registry study (eXpeRience study: Portuguese analysis; one group)
25	Britton 2012[109]	50	140 weeks (982 days)	Retrospective cohort analysis (one group)
26	Barnes 2012 [110]	136	52 weeks	Retrospective medical records analysis (two groups)
27	Zamora 2013[111]	22	78 weeks	Retrospective study based on electronic medical records of a tertiary hospital (one group)
28	Saji 2014[112]	13	16 weeks	Retrospective study (Japanese article, reviewed by researcher)

4.2 List of relevant randomised controlled trials

The systematic review identified add-on mepolizumab as an intervention in 6 RCT s shown in Table 9.

Table 9 Randomised controlled trials

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
Early studies				
SB-240563/006 (Moderate Asthma Study)	IV Mepolizumab 250mg and 750mg	IV Placebo	Subjects with moderate, persistent asthma	SB-240563/006 Flood-Page P, et al; International Mepolizumab Study Group. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. Am J Respir Crit Care Med. 2007 Dec 1;176(11):1062-71. Epub 2007 Sep 13.
CRT110184 (Proof of concept)	IV Mepolizumab 750mg	IV Placebo	Subjects with refractory eosinophilic asthma and a history of recurrent severe exacerbations	CRT110184 Haldar P, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med. 2009 Mar 5;360(10):973-84.
SB-240563/046 (Proof of concept)	IV Mepolizumab 750mg	IV Placebo	Subjects with prednisolone-dependent asthma and persistent sputum eosinophilia	SB-240563/046 Nair P, et al. Mepolizumab for prednisolone-dependent asthma with sputum eosinophilia. N Engl J Med. 2009 Mar 5;360(10):985-93.
Key phase IIb/III trials				
MEA112997 (DREAM)	IV Mepolizumab 750mg IV Mepolizumab 250mg IV Mepolizumab 75mg	IV Placebo	Severe Asthma patients with a confirmed history of ≥2 asthma exacerbations in the past 12 months. who had one or more of the following criteria: - an elevated peripheral blood eosinophil level of ≥300 cells/μL, - sputum eosinophils ≥3%, - FeNO ≥50 ppb and/or - prompt deterioration of asthma control following a 25% reduction in regular maintenance dose of ICS or OCS.	NCT01000506 https://clinicaltrials.gov/ct2/show/NCT01000506?term=Mepolizumab&rank=2 Pavord ID, Howarth P, Bleecker ER et al Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. http://www.ncbi.nlm.nih.gov/pubmed/22901886 Lancet 2012 18;380(9842):651-9
MEA115588 (MENSA)	IV Mepolizumab 75mg SC Mepolizumab	IV and SC Placebo	Severe Asthma patients on high dose ICS, a blood eosinophil level of ≥300 cells/μL that was related to asthma within the 12 months prior to Visit 1 or	NCT01691521 https://clinicaltrials.gov/ct2/show/NCT01691521?term=Mepolizumab&rank=3

	100mg		eosinophil level of ≥150 cells/μL at Visit 1 and a history of 2 exacerbations requiring treatment with systemic steroids in previous year.	Ortega HG, Liu MC, Pavord ID et al Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma. N Engl J Med 2014; 371:1198-1207
MEA115575 (SIRIUS)	SC Mepolizumab 100mg	SC Placebo	Severe Asthma patients on high dose ICS and OCS for ≥6 months, a blood eosinophil level of ≥300 cells/μL that was related to asthma within the 12 months prior to Visit 1 or eosinophil level of ≥150 cells/μL at Visit 1	NCT01691508 https://clinicaltrials.gov/ct2/show/NCT01691508?term=Mepolizumab&rank=9 Bel EH, Wenzel SE, Thompson PJ et al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. N Engl J Med 2014; 371:1189-1197

The clinical effectiveness section will focus on two phase III clinical trials that support the efficacy and safety of mepolizumab in the GSK proposed population for NICE guidance, MENSA and SIRIUS (MEA115588 and MEA115575). Four early studies were considered less relevant for the following reasons:

1. Moderate Asthma Study: SB-240563/006 studied a moderate asthma population not included in the licensed population and did not show a benefit of mepolizumab for the primary endpoint peak expiratory flow (Flood-Page 2007)[113]. However, the study indicated the need for targeting a more severe population that was experiencing frequent exacerbations along with the use of a biomarker of eosinophilic inflammation, such as sputum or peripheral blood eosinophils.

2. Proof-of-concept Exacerbation Study: As a consequence of CRT110184 (Haldar 2009)[52] was an investigator-supported, proof-of-concept study conducted in subjects with severe eosinophilic asthma and a history of recurrent severe exacerbations. It demonstrated a significant decrease in exacerbation frequency with 4-weekly administration of mepolizumab 750 mg IV compared with placebo over a 52-week treatment period (Haldar 2009)[52] and led to the phase IIb /III clinical trial program. However, the study included patients selected on sputum eosinophil count and used an unlicensed dose and posology. Thus, as a proof-of concept study, it was deemed less relevant for the decision problem. The published peer reviewed paper will be provided.

3. Proof-of-concept OCS Reduction Study: Again as a result of the Moderate Asthma Study findings, SB-240563/046 (Nair 2009)[54] was a 26-week, investigator-supported, proof-of-concept study that assessed the ability of mepolizumab 750 mg IV to allow prednisolone dose reduction in subjects with prednisolone-dependent asthma, without inducing an exacerbation. Subjects in the mepolizumab 750 mg IV group were able to reduce their maintenance OCS dose to a greater extent than subjects on placebo while maintaining asthma control (Nair 2009)[54] and further supported the phase III clinical trial program. Again, the study included patients selected on sputum eosinophil count and used an unlicensed dose and posology. Thus, as proof-of concept study, it was deemed less relevant for the decision problem. The published peer reviewed paper will be provided.

4. DREAM, a dose ranging study, confirmed 75mg IV as an appropriate dose. It had 4 inclusion criteria by which patients could enter the trial (see section 4.2). Modelling identified 1 of the 4, blood eosinophil count as a valid marker of predicting response to mepolizumab. Thus, it identified a patient responder population for add-on mepolizumab therapy (see section 4.7).

The appropriate population and dose, identified in DREAM, was taken forward in phase III studies MENSA and SIRIUS. In addition, MENSA confirmed bioequivalence between doses 75mg IV and 100mg SC (see section 4.7.3). This submission will therefore focus on the Phase III results in an appropriate patient population (Section 4.7). However, for completeness and as relevant for parts of the discussion on patient population and quality of life, DREAM's method will be addressed in sections 4.3 to 4.6, efficacy results will be disclosed as part of the meta-analysis of DREAM and MENSA presented in section 4.9 and quality of life measure discussions will be covered in section 4.7 and 4.13.

4.3 Summary of methodology of the relevant randomised controlled trials

4.3.1 Methodology of relevant Randomised Controlled Trials

Two Phase III studies, MENSA and SIRIUS are considered primary efficacy studies for mepolizumab in severe refractory eosinophilic asthma. There were a large number of endpoints for each of the studies, however only those relevant to the decision problem and discussed in the results section 4.7 will be presented below. Further details of each of the studies, including endpoints, can be found in the clinical study reports (CSRs). For completeness sections 4.3 to 4.6 will include an outline of phase IIb and III studies, DREAM, MENSA and SIRIUS. As MENSA and SIRIUS (phase III) are considered the most relevant studies for the decision problem, the results are discussed in context of the GSK proposed population for which guidance is sought in section 4.7. The results of the earlier phase IIb study, DREAM are included in a meta-analysis of DREAM and MENSA in section 4.9.

4.3.1.1 DREAM

Trial design: DREAM was a double-blind, placebo-controlled, parallel-group, 52-week dose-ranging study. Patients were randomly assigned to receive either 75mg or 250mg or 750mg IV mepolizumab or matched placebo in a 1:1:1:1 ratio. The randomisation was stratified on the basis of whether the patient required daily treatment with oral corticosteroids. Randomisation was performed with the use of a centralised computer-generated, permuted-block schedule. The study aimed to randomise at least 151 subjects per group.

Eligibility criteria: Subjects were male or female and aged ≥12 years with a minimum weight of 45kg, but in countries where local regulations or the regulatory status of study medication permitted enrolment of adults only, subjects were ≥18 years. All subjects had severe refractory asthma for ≥12 months prior to Visit 1 and also required regular treatment with a high dose ICS (≥880 mcg/day [ex-actuator] Fluticasone Propionate [FP] or equivalent) with or without maintenance OCS in the 12 months prior to Visit 1. Patients were also required to have need for additional maintenance treatment(s) (e.g., long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], or theophylline) in the 12 months prior to Visit 1. The criteria also included subjects with persistent airflow obstruction as indicated by a pre-bronchodilator FEV_1 <80% predicted recorded at Visit 1 or Visit 2 or peak flow diurnal variability of >20% on 3 or more days during the run-in period.

Subjects were required to have airway inflammation which was likely to be eosinophilic in nature. Eosinophilic airway inflammation could be demonstrated at screening, or documented in the previous 12 months, by one of the following characteristics:

- An elevated peripheral blood eosinophil level of ≥300 cells/μL or
- Sputum eosinophils ≥3% or
- Exhaled nitric oxide (FeNO) ≥50 ppb or

- Prompt deterioration of asthma control (based on documented clinical history or objective measures) following a ≤25% reduction in regular maintenance dose of inhaled or oral corticosteroid dose in the previous 12 months.

Patients were required to have a history of two or more asthma exacerbations requiring treatment with oral or systemic corticosteroids in the 12 months prior to Visit 1, despite the use of high-dose ICS and additional maintenance treatment(s).

There were also defined criteria whereby subjects became ineligible for this study. This included subjects that were current smokers or with a smoking history of >10 pack years (number of pack years = (number of cigarettes per day/20) x number of years smoked), parasitic infection in the 6 months before the study entry, substantial uncontrolled co-morbidity, possibility of pregnancy, and history of poor treatment adherence. Full details of the inclusion and exclusion criteria can be found in the CSR.[114]

Setting and location: There were a total of 81 centres in 13 countries: 17 in the USA, 9 in Germany, 8 in Russia, 7 in Ukraine, 5 in Australia, Canada, France, Poland, Romania and the UK, 4 in Argentina and Chile, and 2 in South Korea. First subject first visit occurred on the 9th November 2009 and the last subject's last visit occurred on the 5th December 2011. There were a total of 33 subjects from the 5 centres within the UK, which represented 5% of the total ITT population.

Intervention: The subjects in this study were randomised to receive mepolizumab at doses of 75mg, 250mg or 750mg or placebo IV once every 4 weeks over a 52-week treatment period in adult and adolescent patients with severe refractory eosinophilic asthma.

The study drugs were prepared by site staff who were aware of the study group assignments but were not involved in study assessments. Mepolizumab and placebo were identical in appearance and were administered by a staff member who was unaware of the study group assignments. The blindness of those involved in the evaluation of the study was maintained at all times.

Permitted medications: Additional asthma medications such as theophyllines or LTRAs were permitted provided they had been taken regularly in the 12 months prior to randomisation (Visit 2, week 0). Maintenance OCS were permitted providing at least one of the exacerbations in the previous 12 months had occurred while the subject was receiving OCS and had been treated with a two-fold or greater increase in the dose of OCS.

Prohibited medications: The following medications were not allowed prior to the screening visit and throughout the study (Table 10):

Table 10 Prohibited Medications (DREAM)

Medication	Washout time prior to screening visits
Investigational drugs	1 month (or five half-lives)
Corticosteroids intra-articular, short-acting intramuscular	1 month
Corticosteroids intramuscular, long-acting depot	3 months

Experimental anti-inflammatory drugs (non-biologics)	3 months
Methotrexate, troleandomycin, oral gold, cyclosporine, azathioprine	3 months
Omalizumab (Xolair) or other biologicals for the treatment of inflammatory conditions	130 days
Chemotherapy/radiotherapy	12 months
Regular oral or systemic corticosteroids for the treatment of conditions other than asthma	12 months

Primary Efficacy Endpoints

The primary efficacy endpoint was frequency of clinically significant exacerbations of asthma. This was defined as the worsening of asthma which in the investigator's opinion required use of oral/systemic corticosteroids and/or hospitalisation and/or emergency department (ED) visits. Use of systemic corticosteroids was defined as IV or oral steroid (e.g., prednisolone) for at least 3 days or a single IM dose. For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days was required.

In order to provide an objective assessment of the circumstances linked to the clinical decision that defined asthma exacerbations, the investigator was to take into account changes from baseline on one or more of the following parameters: a decrease in morning peak flow; an increase in the use of rescue medication; increases in the frequency of nocturnal awakening due to asthma symptoms requiring rescue medication use; an increase in overall asthma symptom score. For subjects who withdrew prematurely from the study all data up to the time of discontinuation were included.

Secondary Efficacy Endpoints

Key secondary endpoints were defined as follows:

- Frequency of exacerbations requiring hospitalisation (including intubation and admittance to an intensive care unit) or ED visits
- Frequency of exacerbations requiring hospitalisation only
- Mean change from baseline in clinic pre-bronchodilator FEV_1 at week 52
- Mean change from baseline in Asthma Control Questionnaire (ACQ) score at week 52
- Mean change in Asthma Quality of Life Questionnaire (AQLQ) score from baseline

Other Efficacy Endpoints

- Subject Rated Response to Therapy
- Clinician Rated Response to Therapy
- Mean change in EQ-5D health outcomes questionnaire score from baseline

For validity of health outcome measures please refer to Section 4.7.

Safety Endpoints: AEs, clinical laboratory tests, vital signs, and 12-lead ECGs. Blood samples were obtained for immunogenicity, pharmacokinetic, and pharmacodynamic assessments.

For a complete list of endpoints, please refer to the CSR.[114]

4.3.1.2 MENSA

Trial design: MENSA was a double-blind, double-dummy, placebo-controlled, parallel-group, 32-week study evaluating the effects of mepolizumab 75mg IV and 100mg SC adjunctive therapy in subjects with severe refractory eosinophilic asthma. Patients were randomly assigned to receive either 75mg IV or 100mg SC mepolizumab or matched placebo in a 1:1:1 ratio. Randomisation was performed with the use of a centralised computer-generated, permuted-block schedule. The study aimed to randomise at least 180 subjects per group (see below).

Eligibility Criteria: The inclusion criteria were the same as DREAM (subjects with severe asthma and a history of 2 or more exacerbations in the previous 12 months), except airway inflammation had to be characterised as eosinophilic in nature by one of the following:

- An elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past 12 months prior to Screening or
- An elevated peripheral blood eosinophil count of ≥150 cells/μL at screening.

Further details of this can be found in the CSR for this study.[115]

Setting and location: A total of 119 centres in 16 countries randomised and treated subjects: 18 in the USA and Japan, 11 in the Republic of Korea, 10 in Canada and Germany, 8 in France and Italy, 7 in Argentina, 5 in Spain and Ukraine, 4 in Belgium, the Russian Federation and the UK, 3 centres in Australia and Chile, and 1 in Mexico. The study was initiated on 8 October 2012 (first subject screened) and was completed on 18 January 2014 (last subject last visit). There were a total of 17 subjects from the 4 centres within the UK, which represented 5% of the total ITT population.

Intervention: Patients were randomly assigned to receive mepolizumab, which was administered as either a 75mg IV dose or a 100mg SC dose, or placebo every 4 weeks for 32 weeks.

The study drugs were prepared by site staff who were aware of the study group assignments but were not involved in study assessments. Mepolizumab and placebo were identical in appearance and were administered by a staff member who was unaware of the study group assignments. The blindness of those involved in the evaluation of the study was maintained at all times.

Permitted medications: Additional asthma medications such as theophyllines or LTRAs were permitted provided they had been taken regularly in the 3 months prior to randomisation (Visit 2, Week 0). Maintenance OCS was permitted.

Continuous Positive Airway Pressure (CPAP) for the treatment of obstructive sleep apnoea was permitted, if initiated prior to the Screening Visit.

Prohibited medications: The following medications were not allowed prior to the screening visit and throughout the study (Table 11):

Table 11 Prohibited Medications (MENSA and SIRIUS)

Medication	Washout time prior to screening visit
Investigational drugs	1 month or 5 half-lives whichever is longer
Omalizumab (Xolair)	130 days
Other monoclonal antibodies	5 half-lives
Experimental anti-inflammatory drugs (non biological)	3 months
Immunosuppressive medications such as those listed below (not all inclusive)	
Corticosteroids intramuscular, long-acting depot if used to treat a condition other than asthma	3 months
Methotrexate, troleandomycin, cyclosporin, azathioprine	1 month
Oral gold	3 months
Chemotherapy used for conditions other than asthma	12 months
Regular systemic (oral or parenteral) corticosteroids for the treatment of conditions other than asthma	3 months

Primary Efficacy Endpoint

The primary efficacy endpoint was the frequency of clinically significant exacerbations of asthma as defined by worsening of asthma which required use of systemic corticosteroids and/or hospitalisation and/or Emergency Department (ED) visits. Use of systemic corticosteroids was defined as IV or oral steroid (e.g., prednisolone) for at least 3 days or a single IM dose. For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days was required.

In order to provide an objective assessment of the circumstances linked to the clinical decision that defined asthma exacerbations, the investigator took into account changes on one or more of the following parameters: decrease in morning peak flow, increase in the use of rescue medication, increase in the frequency of nocturnal awakening due to asthma symptoms requiring rescue medication use, and increase in overall asthma symptom score.

Secondary Efficacy Endpoints

- Frequency of exacerbations requiring hospitalisation (including intubation and admittance to an ICU) or ED visits
- Frequency of exacerbations requiring hospitalisation
- Mean change from baseline in clinic pre-bronchodilator FEV_1 at Week 32
- Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) at Week 32

Other Efficacy Endpoints:

- Mean change from baseline in Asthma Control Questionnaire (ACQ-5) score at Week 32
- Subject Rated Response to Therapy
- Clinician Rated Response to Therapy
- Mean change from baseline in clinic post-bronchodilator FEV_1 at Week 32
- Work Productivity and Activity Impairment Index: General Health (WPAI:GH)
- Resource utilisation measures

Safety Endpoints: AEs, clinical laboratory tests, vital signs, and 12-lead ECGs. Blood samples were obtained for immunogenicity, pharmacokinetic, and pharmacodynamic assessments.

For a complete list of endpoints, please refer to the CSR.[115]

4.3.1.3 SIRIUS

Trial design: SIRIUS was a 24-week, double-blind, placebo-controlled parallel group study with four phases: 1) OCS Optimisation, 2) Induction, 3) OCS Reduction and 4) Maintenance. The OCS Optimisation Phase was a run-in phase intended to assure that patients entered the double-blind treatment phase on the lowest dose of prednisolone that would maintain asthma control. Patient's asthma status was assessed weekly; the lowest effective prednisolone dose was defined as the dose the patient was taking prior to the emergence of asthma symptoms or the occurrence of an exacerbation. The Induction Phase was designed to allow for sufficient time for those patients randomised to the mepolizumab arm to achieve a decrease in eosinophilic inflammation prior to the reduction in prednisolone. During the OCS Reduction Phase, patients received four additional doses of double-blind study treatment. Patients were assessed for prednisolone reduction every 4 weeks. Prednisolone dose titrations in the Optimisation and Reduction phases followed pre-specified algorithms. Patients were maintained during the last 4 weeks of the study without any further prednisolone dose adjustment (i.e., Maintenance Phase).

Patients were randomly assigned to receive either 100mg SC mepolizumab or matched placebo in a 1:1 ratio. The study aimed to randomise at least 60 subjects per group.

Eligibility Criteria: Patients ≥12 years of age with severe eosinophilic asthma, a pre-bronchodilator FEV_1 <80% predicted, and a documented requirement for regular treatment with maintenance systemic corticosteroids (5.0 to 35 mg/day prednisolone or equivalent) and high-dose ICS (≥880 mcg/day [ex-actuator] FP or equivalent) were eligible. At the end of the run-in period, patients were eligible to be randomised if they had achieved a stable dose of OCS during the Optimisation Phase.

Airway inflammation had to be characterised as eosinophilic in nature by one of the following:

- An elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past 12 months prior to Screening or

- An elevated peripheral blood eosinophil count of ≥150 cells/μL during the optimisation phase

The criteria by which patients were not eligible were very similar to the DREAM and MENSA studies. Further details of this can be found in the CSR for this study.[51]

Setting and location: The ITT Population was comprised of subjects from 38 centres in 10 countries: 8 in Germany, 5 in the Czech Republic, France and the USA, 4 in the UK, 3 in Australia and Canada, 2 in the Netherlands and Poland, and 1 in Mexico. There were a total of 10 subjects from the four centres within the UK, which represented 7% of the total ITT population.

Intervention: Mepolizumab 100 mg SC compared with placebo over a 24-week treatment period in adult and adolescent patients with severe eosinophilic asthma. Time of administration: 4 weekly SC injections.

The study drugs were prepared by site staff who were aware of the study group assignments but were not involved in study assessments. Mepolizumab and placebo were identical in appearance and were administered by a staff member who was unaware of the study group assignments. The blindness of those involved in the evaluation of the study was maintained at all times.

Prednisolone use was captured on a daily basis by each subject through the use of a daily eDiary. Site designated staff reviewed information to determine if subjects were taking the prednisolone dose instructed by the protocol and followed up with the subject accordingly.

Permitted medications: Maintenance OCS was required per study eligibility criteria. OCS dose adjustments that occurred during the study were recorded.

Additional asthma medications such as theophylline or LTRAs were permitted provided they had been taken regularly in the 3 months prior to randomisation (Visit 3).

Continuous positive airway pressure (CPAP) for the treatment of obstructive sleep apnoea was permitted, if initiated prior to the Visit 1 (Screening Visit).

Prohibited medications: OCS (prednisolone) was supplied for use for the treatment of asthma. During this study, only the study supplied prednisolone could be used for the treatment of asthma. The medications not allowed prior to screening or during the study were the same as those in the MENSA trial (Table 11).

Primary Efficacy Endpoint

Percent reduction of OCS dose during Weeks 20-24 compared with the baseline dose, while maintaining asthma control, categorised as follows:

- 90% to 100%
- 75% to <90%
- 50% to <75%
- >0% to <50%
- No decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment.

Secondary Efficacy Endpoints

During Weeks 20-24, while maintaining asthma control:

- Proportion of subjects who achieved a reduction of ≥50% in their daily OCS dose, compared with baseline dose
- Proportion of subjects who achieved a reduction of OCS dose to ≤5.0 mg
- Proportion of subjects who achieved a total reduction of OCS dose
- Median percentage reduction from baseline in daily OCS dose.

Other Efficacy Endpoints

- Rate of clinically significant exacerbations
- Rate of exacerbations requiring hospitalisation or ED visits
- Rate of exacerbations requiring hospitalisation
- Mean change from baseline in clinic pre-bronchodilator FEV_1 and in clinic post-bronchodilator FEV_1 at Week 24
- Mean change from baseline in ACQ-5 score at Week 24
- Mean change from baseline in SGRQ at Week 24
- Work Productivity and Activity Impairment Index: General Health (WPAI:GH)
- Resource utilisation measures

Safety Endpoints: AEs, including both systemic (i.e., allergic/IgE-mediated and non-allergic) and local site reactions, clinical laboratory tests, including assessment of immunogenicity, vital signs, and 12-lead ECGs.

For a complete list of endpoints, please refer to the CSR.[51]

4.3.2 Comparative summary of methodology

A summary of these studies can be found below in Table 12.

Table 12 Comparative summary of trial methodology

Trial number	DREAM	MENSA	SIRIUS
Location	81 centres in 13 countries including Argentina, Australia, Canada, Chile, France, Germany, South Korea, Poland, Romania, Russia, Ukraine, United Kingdom and the USA.	119 centres in 16 countries including Argentina, Australia, Belgium, Canada, Chile, France, Germany, Italy, Japan, Republic of Korea, Mexico, Russian Federation, Spain, Ukraine, UK and the USA.	38 centres in 10 countries including Australia, Canada, Czech Republic, France, Germany, Mexico, Netherlands, Poland, UK and the USA.
Trial design	Randomised, Double-blind, Placebo-controlled, Parallel-group, Dose-ranging	Randomised, Double-blind, Double-dummy, Placebo-controlled, Parallel-group	Randomised, Double-blind, Placebo-controlled, Parallel-group
Eligibility criteria for participants	Patients with severe asthma, aged ≥12 years with a requirement for regular treatment with high dose ICS with or without maintenance OCS, in the previous 12 months. Patients were also required to have need for additional maintenance treatment(s) (e.g., LABA, LTRA, or theophylline) and evidence of eosinophilic airways inflammation. Eosinophilic airway inflammation could be demonstrated at screening, or documented in the previous 12 months, by one of the following characteristics: • An elevated peripheral blood eosinophil level of ≥300 cells/μL *or* • Sputum eosinophils ≥3% *or* • Exhaled nitric oxide (FeNO) ≥50 ppb *or* • Prompt deterioration of asthma control (based on documented clinical history or objective measures) following a ≤25% reduction in regular maintenance dose of inhaled or oral corticosteroid dose in the previous 12 months. Patients further were required to have a pre-bronchodilator FEV_1 <80% predicted and a history of two or more asthma exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to Visit 1, despite the use of high-dose	The inclusion criteria were the same as the DREAM Study, except airway inflammation had to be characterised as eosinophilic in nature by one of the following: An elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past 12 months prior to Screening or an elevated peripheral blood eosinophil count of ≥150 cells/μL at screening.	Patients ≥12 years of age with severe eosinophilic asthma, a pre-bronchodilator FEV_1 <80% predicted, and a documented requirement for regular treatment with maintenance systemic corticosteroids (5.0 to 35 mg/day prednisolone or equivalent) and high-dose ICS (≥880 mcg/day [ex-actuator] FP or equivalent) were eligible. At the end of the run-in period, patients were eligible to be randomised if they had achieved a stable dose of OCS during the Optimisation Phase. Airway inflammation had to be characterised as eosinophilic in nature by one of the following: • An elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past12 months prior to Screening or • An elevated peripheral blood eosinophil count of ≥150 cells/μL during the optimisation phase

	ICS.		
Trial drugs Intervention(s) (n=[x]) and comparator(s) (n=[x]) **Permitted and disallowed concomitant medication**	Mepolizumab 75mg IV (n=153) Mepolizumab 250mg IV (n=152) Mepolizumab 750mg IV (n=156) Placebo IV (n=155) The timing of assessments schedule can be found in the CSR. Permitted medications: Additional asthma medications such as theophyllines or LTRAs were permitted provided they had been taken regularly in the 3 months prior to randomisation (Visit 2, Week 0). Maintenance OCS was permitted. Continuous Positive Airway Pressure (CPAP) for the treatment of obstructive sleep apnoea was permitted, if initiated prior to the Screening Visit. Prohibited medications: Refer to Table 10.	Mepolizumab 75mg IV + Placebo SC (n=191) Mepolizumab 100 SC+ Placebo IV (n=194) Placebo SC & IV (n=191) The timing of assessments schedule can be found in the CSR. Permitted medications were the same as DREAM. Prohibited medications: Refer to Table 11.	Mepolizumab 100mg SC (n=69) Placebo SC (n=66) The timing of assessments schedule can be found in the CSR. Permitted medications: Maintenance OCS was required per study eligibility criteria. OCS dose adjustments that occurred during the study were recorded in the eCRF. Additional asthma medications such as theophylline or LTRA were permitted provided they had been taken regularly in the 3 months prior to randomisation (Visit 3). CPAP for the treatment of obstructive sleep apnoea was permitted, if initiated prior to the Visit 1 (Screening Visit). At the end of the study (Week 24), subjects who did not enter the OLE study were prescribed appropriate alternative asthma therapy if needed and as determined by the study investigator. Prohibited medications: Refer to Table 11.

Primary outcomes	**Clinically significant asthma exacerbations** Frequency of clinically significant exacerbations of asthma as defined by worsening of asthma which required use of systemic corticosteroids and/or hospitalisation and/or emergency department (ED) visits. Use of systemic corticosteroids was defined as IV or oral steroid (e.g., prednisolone) for at least 3 days or a single IM dose.	**Clinically significant asthma exacerbations** Frequency of clinically significant exacerbations of asthma as defined by worsening of asthma which required use of systemic corticosteroids and/or hospitalisation and/or emergency department (ED) visits. Use of systemic corticosteroids was defined as IV or oral steroid (e.g., prednisolone) for at least 3 days or a single IM dose.	**Reduction of OCS** Percent reduction of OCS dose during Weeks 20-24 compared with the baseline dose, while maintaining asthma control, categorised as follows: • 90% to 100% • 75% to <90% • 50% to <75% • >0% to <50% • No decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment.
Secondary/ other outcomes	**Secondary:** • Frequency of exacerbations requiring hospitalisation (including intubation and admittance to an intensive care unit) or ED visits • Mean change from baseline in clinic pre-bronchodilator FEV_1 at week 52 • Mean change from baseline in Asthma Control Questionnaire (ACQ) score at week 52 • Mean change in Asthma Quality of Life Questionnaire (AQLQ) score from baseline at week 52 **Other Efficacy Endpoints:** • Subject Rated Response to Therapy • Clinician Rated Response to Therapy • Mean change in EQ-5D health outcomes questionnaire score from baseline	**Secondary:** • Frequency of exacerbations requiring hospitalisation (including intubation and admittance to an ICU) or ED visits • Frequency of exacerbations requiring hospitalisation • Mean change from baseline in clinic pre-bronchodilator FEV_1 at Week 32 • Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) at Week 32 **Other Efficacy Endpoints:** • Mean change from baseline in Asthma Control Questionnaire (ACQ-5) score at Week 32 • Subject Rated Response to Therapy • Clinician Rated Response to Therapy • Mean change from baseline in clinic post-bronchodilator FEV_1 at Week 32 • Work Productivity and Activity Impairment Index: General Health (WPAI:GH) • Resource utilisation measures	**Secondary:** • Proportion of subjects who achieved a reduction of ≥50% in their daily OCS dose, compared with baseline dose • Proportion of subjects who achieved a reduction of OCS dose to ≤5.0 mg • Proportion of subjects who achieved a total reduction of OCS dose • Median percentage reduction from baseline in daily OCS dose. **Other Efficacy Endpoints:** • Rate of clinically significant exacerbations • Rate of exacerbations requiring hospitalisation or ED visits • Rate of exacerbations requiring hospitalisation • Mean change from baseline in clinic pre-bronchodilator FEV_1 and in clinic post-bronchodilator FEV_1 at Week 24 • Mean change from baseline in ACQ-5 score at Week 24 • Mean change from baseline in SGRQ at Week 24

			• Work Productivity and Activity Impairment Index: General Health (WPAI:GH) • Resource utilisation measures
Pre-planned subgroups (Further details found in the CRS for each study)	• Presence of each of the eosinophilic airways inflammation inclusion criteria • Age • Gender • Baseline percentage predicted pre-bronchodilator FEV_1 • Number of exacerbations in the year prior to the study • Region • Baseline use of maintenance oral corticosteroids (use vs. no use) • Baseline blood eosinophil count • Baseline total IgE concentration	• Age • Gender • Weight • Baseline Percent Predicted Pre-Bronchodilator FEV_1 • Number of Exacerbations in the year prior to the study • Region • Baseline Maintenance Oral Corticosteroid Therapy • Baseline Blood Eosinophil count • Baseline IgE Concentration • Prior Use of Xolair	• Duration of Prior OCS Use • Baseline OCS Dose • Geographic Region • Baseline Blood Eosinophil count • Gender • Weight

*For further details regarding the scoring methods, refer to section 4.4 (Statistical analysis and definition of study groups in the relevant randomised controlled trials), and for further details regarding timing of assessments please refer to the CSR for each study.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

4.4.1 Statistical analyses of RCTs

In this section, the statistical analyses for each of the studies, DREAM, MENSA and SIRIUS, will be outlined. Sample size assumptions as well as any planned analyses will also be detailed.

4.4.1.1 DREAM

Sample size assumptions

A total of 151 randomised subjects per arm was estimated to give 90% power to detect a decrease in the exacerbation rate from 1.5 per year on placebo to 0.9 per year on mepolizumab (a 40% decrease) at the 2-sided 5% significance level.

This assumed the number of exacerbations per year followed a negative binomial distribution with a dispersion parameter k=0.7 and assumed that 15% of patients would withdraw from the study.

Planned analyses

Interim analysis - No interim analysis was planned.

Final analysis - The rate of clinically significant exacerbations was analysed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable) and baseline percent predicted pre-bronchodilator FEV_1, with logarithm of time on treatment as an offset variable.

For the primary endpoint of exacerbations, for patients who withdrew, all data up to the time of patient withdrawal were included in the analyses. However, there are missing data for the period following withdrawal. The primary analysis made a standard assumption known as the Missing At Random (MAR) assumption. This assumes that future exacerbations for those who withdraw can be predicted from their exacerbation history prior to withdrawal and from the exacerbation rate of similar patients on the same treatment.

The rate of exacerbations requiring hospitalisation or ED visits were analysed as above for rate of clinically significant exacerbations. Analysis of FEV_1, ACQ scores and AQLQ scores were performed using mixed model repeated measures methods (including covariates as above plus baseline value), visit and interaction terms for visit by baseline, and visit by treatment group.

A closed testing procedure was used to ensure strong control of the type I error in adjusting for multiplicity across treatment comparisons and primary and secondary endpoints. Following an initial test for a linear trend of decrease in exacerbation rate with increasing dose of mepolizumab at a two-sided α=5% level, each dose of

mepolizumab (75, 250, and 750 mg IV) was compared with placebo using a one-sided Hochberg testing procedure with a one-sided α=2.5%. A hierarchical 'gatekeeping' approach was used to control for multiplicity arising from the testing of the primary and secondary endpoints. A step-down testing procedure was applied where inference for an endpoint in the predefined hierarchy was dependent on statistical significance having been achieved for the previous endpoints in the hierarchy. For each endpoint, multiplicity across different treatment comparisons was controlled using the one-sided Hochberg testing procedure. Full details are given in the CSR.[114]

Subgroup examination

Exploratory multivariate modelling was performed to investigate baseline variables predictive of overall number of exacerbations and of differential efficacy of mepolizumab. Baseline covariates considered for inclusion were age, sex, weight, baseline % predicted pre-bronchodilator FEV_1, number of exacerbations in the year prior to screening (i.e., 2, 3, 4+), region, baseline use of maintenance oral corticosteroids, airway reversibility, blood eosinophil count and baseline total IgE concentration. In particular the potential differential effect of mepolizumab on the exacerbation rate according to baseline blood eosinophils was investigated.

Consistency of treatment effect for covariates fitted in the primary efficacy endpoint analysis model were examined by fitting separate additional models to examine treatment effect according to each of the following subgroups: region, age, sex, baseline pre-bronchodilator % predicted FEV_1, exacerbations in the year prior to the study, race, baseline OCS therapy (OCS vs. no OCS), reversibility at screening and baseline blood eosinophils.

Further subgroup analysis of the primary endpoint was performed to investigate the potential differential effects of mepolizumab according to each of the possible airway inflammation characteristics (recorded in the previous 12 months) i.e.

- Peripheral blood eosinophil level of ≥300 cells/μL that is related to asthma
- Sputum eosinophils ≥3%
- Exhaled nitric oxide ≥50 ppb (at Visit 1 or Visit 2)
- Prompt deterioration of asthma control (based on documented clinical history or objective measures) following a ≤25% reduction in regular maintenance dose of inhaled or oral corticosteroid dose.

For patients included in the sputum sub study, subgroup analysis of the primary endpoint was performed according to whether their baseline sputum eosinophils are ≥3%.

No formal hypothesis testing in sub-groups of the populations was performed.

4.4.1.2 MENSA

Sample size assumptions

A study with 180 subjects randomised to each treatment arm was estimated to have over 90% power to detect a 40% decrease in the exacerbation rate from 2.4 per annum (p.a.) on placebo to 1.44 p.a. on each of the mepolizumab treatment arms using a two sided 5% significance level.

The calculation assumed the number of exacerbations per year followed a negative binomial distribution with a dispersion parameter k=0.8.

Planned analyses

Interim analysis - An Independent Data Monitoring Committee (IDMC) ensured external objective review of safety issues. The IDMC reviewed cardiovascular adverse events and all cause mortality from MENSA and SIRIUS and from the open label safety studies MEA115661 (COSMOS) and MEA115666 (COLUMBA). The unblinded statistical analyses were performed by an independent Statistical Data Analysis Centre (SDAC) at Duke University, NC. Unblinded results were not available to the study team: The SDAC communicated directly with the IDMC, and IDMC recommendations were made to a primary contact that was external to the mepolizumab study team(s) at GSK.

There were no circumstances under which IDMC review of the data would lead to a recommendation to stop due to efficacy of mepolizumab. Therefore no adjustment to the final alpha level for efficacy was made based on the safety stopping guidelines.

Final analysis - The rate of clinically significant exacerbations was analysed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable) and baseline percent predicted pre-bronchodilator FEV_1, with logarithm of time on treatment as an offset variable.

For the primary endpoint of exacerbations, for patients who withdrew, all data up to the time of patient withdrawal were included in the analyses. Sensitivity analyses to investigate alternative assumptions regarding missing data were performed in the same way as described above for DREAM.

The rate of exacerbations requiring hospitalisation or ED visits and the rate of exacerbations requiring hospitalisation was analysed as above for rate of clinically significant exacerbations. Analysis of FEV_1 was performed using mixed model repeated measures methods (including covariates as above plus baseline value), visit and interaction terms for visit by baseline, and visit by treatment group. Analysis of SGRQ was performed using analysis of covariance with covariates as above plus baseline value.

A closed testing procedure was used to ensure strong control of the type I error in adjusting for multiplicity across treatment comparisons and primary and secondary endpoints. Each dose (75 mg IV and 100 mg SC) was compared with placebo using a one-sided Hochberg testing procedure with a one-sided α=2.5%. A hierarchical 'gatekeeping' approach was used to control for multiplicity arising from the testing of the primary and secondary endpoints. A step-down testing procedure was applied where inference for an endpoint in the predefined hierarchy was dependent on

statistical significance having been achieved for the previous endpoints in the hierarchy. For each endpoint, multiplicity across different treatment comparisons was controlled using the one-sided Hochberg testing procedure. Full details are given in the CSR.[115]

Subgroup examination

Exploratory multivariate modelling was performed to investigate baseline variables predictive of overall number of exacerbations and of differential efficacy of mepolizumab. It was planned that if the mepolizumab IV and SC treatment groups produced similar results in the primary analysis then these treatment arms would be combined in this modelling analysis.

Baseline covariates considered for inclusion were age, sex, weight, baseline % predicted pre-bronchodilator FEV_1, number of exacerbations in the year prior to screening (i.e., 2, 3, 4+), region, baseline use of maintenance oral corticosteroids, airway reversibility, blood eosinophil count and baseline total IgE concentration.

The rate of exacerbations was also tabulated by treatment group according to these covariates. For the multivariate modelling, age, baseline pre-bronchodilator % predicted FEV_1, reversibility at screening, blood eosinophils and total IgE concentration, were each treated as continuous. When presenting tabulations, they were categorised as follows; age (12-17, 18-29, 30-49, 50-64, ≥65), % predicted FEV_1 (≤60%, >60-80%, >80%), baseline reversibility, blood eosinophils (<150, ≥150-<300, ≥300-<500, ≥500 cells/μL) and total IgE concentration (≤ 30, >30-≤700, >700 U/mL).

Further tabulations of the primary endpoint were performed to investigate the potential differential effects of mepolizumab according to a) presence of nasal polyps at screening; b) previous failure on omalizumab (Xolair) (assessed at screening) and c) the two possible protocol inclusion criteria for eosinophilic asthma i.e.

- Peripheral blood eosinophil level of ≥300 cells/μL in the previous 12 months prior to Visit 1 that is related to asthma
- Peripheral blood eosinophil level of ≥150 cells/μL at Visit 1 that is related to asthma

The relationship between these inclusion criteria and to what extent they intersect was also examined.

No formal hypothesis testing in sub-groups of the populations were performed.

4.4.1.3 SIRIUS

Sample size assumptions - The sample-size calculation was based on the proportional-odds model. It was estimated that with a sample of 120 patients, the study would have a power of 90% to detect an increase of 25% in the proportion of patients who had a reduction of 50% or more in the oral steroid dose, at a two-sided 5% significance level. On the assumption that such a reduction would occur in 48% of the patients in the placebo group, the calculation implied that 73% of patients in

the mepolizumab group would have this reduction. These proportions were associated with an odds ratio of 2.9 for a lower category of steroid use in the mepolizumab group, than in the placebo group.

Planned analyses

Interim analysis – As described earlier, an IDMC was also used in SIRIUS to ensure external objective review of safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of data.

Final analysis – The primary efficacy endpoint was the percentage reduction of daily oral steroid dose during weeks 20-24 compared to the dose determined during the optimisation phase, using the following categories: 1) 90-100%, 2) 75-<90% 3) 50-<75%, 4) >0-<50%, and 5) no decrease in oral steroid dose, or lack of control during weeks 20-24 or withdrawal from treatment. Use of the categories enabled greater discrimination of response compared to analysis of proportions achieving a specific reduction and the proportional odds model allowed for covariate adjustment. The primary endpoint was analysed using a proportional odds model for the above categories of oral steroid reduction, with covariates of region, number of years on oral steroids (<5 years versus ≥5 years), and baseline oral steroid dose.

For the primary analysis of OCS reduction, all subjects in the ITT Population were included. Subjects who withdrew early or who had missing data were assigned to the lowest efficacy category.

Sensitivity analysis was performed by assigning subjects to the efficacy category according to the reduction they had obtained by the time of their withdrawal (average dose in the 28 days prior to withdrawal). Subjects withdrawing within 28 days of an exacerbation were included in the lowest efficacy category. This analysis gave a similar result to the primary analysis.

Analysis of the proportion of patients with specific reductions in the oral steroid dose was performed using a binary logistic-regression model with adjustment for covariates. The median percentage reduction in dose was analysed with the use of the Wilcoxon test.

Subgroup examination

Further tabulations of the primary endpoint were performed to investigate the potential differential effects of mepolizumab according to:

a) all covariates in the primary analysis model (for the subgroup analysis by OCS dose at baseline subjects will be grouped as follows: <10mg, ≥10mg- <15mg, ≥15mg-<25mg, ≥25mg prednisolone equivalent dose at baseline but analysed as a continuous variable)

b) baseline blood eosinophils, with subjects grouped as follows: <150, ≥150-<300, ≥300-<500, ≥500 cells/µ/L

c) the two possible protocol inclusion criteria for eosinophilic asthma i.e.

- An elevated peripheral blood eosinophil level of ≥300 cells/μL that was related to asthma within the previous 12 months prior to Visit 3

OR

- Peripheral baseline eosinophil level ≥150 cells/μL between Visit 1 and Visit 3 that was related to asthma

No formal hypothesis testing in sub-groups of the populations was performed.

When carrying out the GSK proposed population analyses, the same statistical analyses methods were used as the primary analyses.

4.4.2 Summary of statistical analyses in RCTs

Details of the statistical tests used in the primary analyses have been outlined in Table 13 below.

Table 13 Summary of statistical analyses used in the RCTs

Trial number	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
DREAM	The study was designed to test superiority of mepolizumab vs. placebo.	**Intent-to-Treat (ITT) Population:** Consisted of all subjects who were randomised and received at least one dose of study medication. **Primary Analysis:** The primary endpoint of rate of clinically significant exacerbations of asthma over the 52 week treatment period was analysed using a negative binomial model, adjusting for, covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable) and baseline percent predicted pre-bronchodilator FEV1, with the log of time followed for exacerbations as an offset variable. These covariates were expected to predict increased frequency of exacerbations.	A total of 151 randomised subjects per arm was estimated to give 90% power to detect a decrease in the exacerbation rate from 1.5 per year on placebo to 0.9 per year on mepolizumab (a 40% decrease) at the 2-sided 5% significance level. This assumed the number of exacerbations per year followed a negative binomial distribution with a dispersion parameter k=0.7 and assumed that 15% of patients would withdraw from the study.	For the primary endpoint of exacerbations, for patients who withdrew, all data up to the time of patient withdrawal were included in the analyses. However, there are missing data for the period following withdrawal. The primary analysis made a standard assumption known as the MAR assumption. This assumes that future exacerbations for those who withdraw can be predicted from their exacerbation history prior to withdrawal and from the exacerbation rate of similar patients on the same treatment. In order to understand how different assumptions regarding missing data could affect the results, two key sensitivity analyses were performed. In both of these sensitivity analyses, it is assumed that future exacerbations for patients who withdrew from a mepolizumab arm could be predicted based on the exacerbation rate in the placebo arm, not on the mepolizumab arm. Both analyses showed similar results to the primary analysis.
MENSA	This study was designed to test the superiority of mepolizumab 75mg IV vs. placebo and the superiority of mepolizumab 100mg SC vs. placebo.	**Intent-to-Treat Population:** Consisted of all subjects who were randomised and received at least one dose of trial medication. **Primary Analysis:** The primary endpoint of rate of clinically significant exacerbations of asthma over the 52 week treatment period was analysed using a negative binomial model, adjusting for, covariates of	A study with 180 subjects randomised to each treatment arm was estimated to have over 90% power to detect a 40% decrease in the exacerbation rate from 2.4 per annum (p.a.) on placebo to 1.44 p.a. on each of the mepolizumab treatment arms using a two sided 5% significance level. The calculation assumed the number of exacerbations per year followed a negative binomial distribution with a dispersion parameter k=0.8.	For the primary endpoint of exacerbations, for patients who withdrew, all data up to the time of patient withdrawal were included in the analyses. However, there are missing data for the period following withdrawal. The primary analysis made a standard assumption known as the MAR assumption. This assumes that future exacerbations for those who withdraw can be predicted from their exacerbation history prior to withdrawal and from the exacerbation rate of

		treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable) and baseline percent predicted pre-bronchodilator FEV_1, with the log of time followed for exacerbations as an offset variable. These covariates were expected to predict increased frequency of exacerbations.		similar patients on the same treatment. In order to understand how different assumptions regarding missing data could affect the results, two key sensitivity analyses were performed. In both of these sensitivity analyses, it is assumed that future exacerbations for patients who withdrew from a mepolizumab arm could be predicted based on the exacerbation rate in the placebo arm, not on the mepolizumab arm. Both analyses showed similar results to the primary analysis.
SIRIUS	This study was designed to test the superiority of mepolizumab 100mg SC vs. placebo.	**Intent-to-Treat (ITT) Population:** Consisted of all subjects who were randomised and received at least one dose of study medication. **Primary Analysis:** The number of subjects in each category for percent reduction of OCS dose during Weeks 20-24 compared with the baseline dose was analysed using a proportional odds model with covariates of treatment, region, duration of OCS use at baseline (<5 years vs. ≥5 years), and dose of OCS at baseline. These covariates were expected to predict the extent to which a patient would be able to reduce their OCS dose.	The sample-size calculation was based on the proportional-odds model. It was estimated that with a sample of 120 patients, the study would have a power of 90% to detect an increase of 25% in the proportion of patients who had a reduction of 50% or more in the oral steroid dose, at a two-sided 5% significance level. On the assumption that such a reduction would occur in 48% of the patients in the placebo group, the calculation implied that 73% of patients in the mepolizumab group would have this reduction. These proportions were associated with an odds ratio of 2.9 for a lower category of steroid use in the mepolizumab group, than in the placebo group.	For the primary analysis of OCS reduction, all subjects in the ITT Population were included. Subjects who withdrew early or who had missing data were assigned to the lowest efficacy category. Sensitivity analysis was performed by assigning subjects to the efficacy category according to the reduction they had obtained by the time of their withdrawal (average dose in the 28 days prior to withdrawal). Subjects withdrawing within 28 days of an exacerbation were included in the lowest efficacy category. This analysis gave a similar result to the primary analysis.

(Details of the statistical analysis for each study can be found in the respective CSRs)

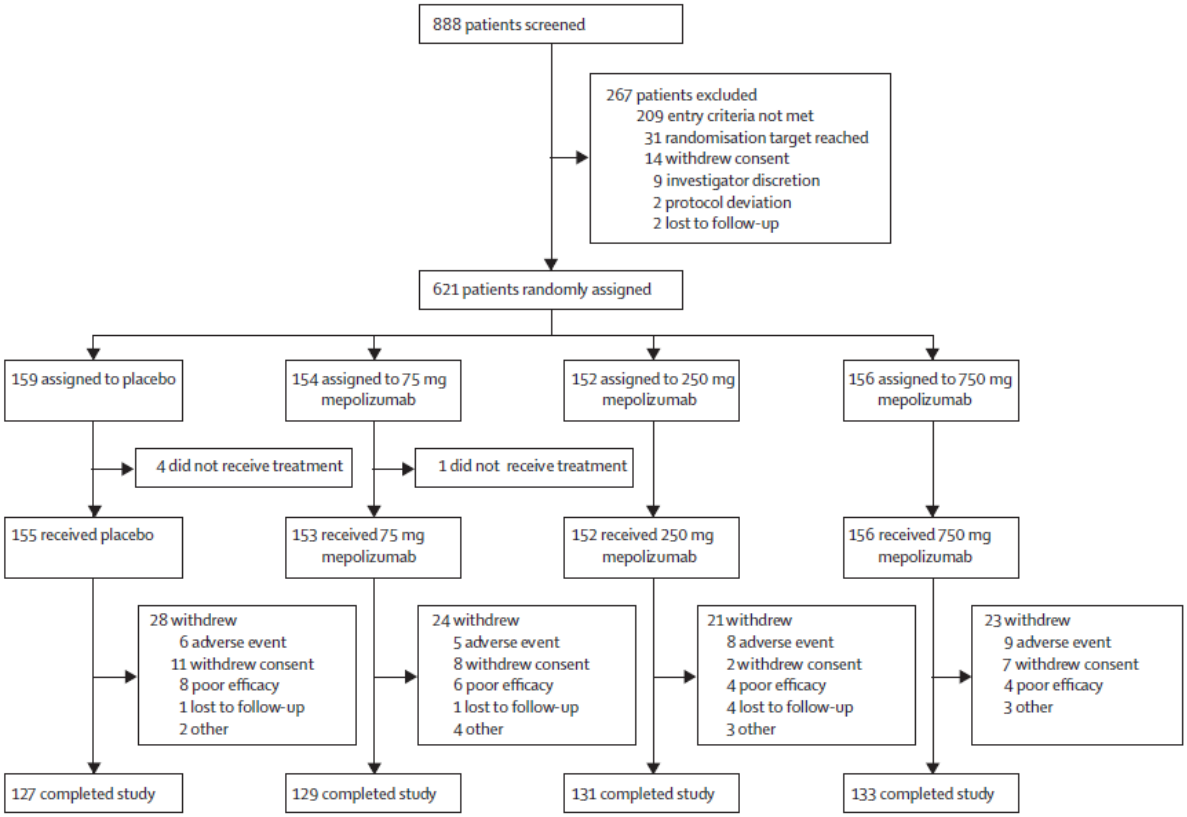
4.5 Participant flow in the relevant randomised controlled trials

4.5.1 Participant flow

4.5.1.1 DREAM

In the DREAM study there were a total of 888 subjects enrolled. Seven hundred and twenty subjects entered run-in, 103 (12%) of enrolled subjects failed and 617 (69%) of enrolled subjects completed run-in. The most frequent reason for failing run-in was that subjects did not meet continuation criteria (75 enrolled subjects [8%]). This is summarised in Figure 4 below.

Figure 4 Trial profile consort diagram (DREAM)



Six hundred and sixteen subjects who were randomised into the study and received treatment are included in the ITT population. Five subjects were randomised in error and did not receive any treatment. These subjects are therefore not included in the ITT population. Of the 888 subjects in the All Subjects Enrolled population, 144 (16%) subjects deviated from criteria at screening and 83 (9%) subjects deviated at randomisation. The most frequent reasons for subjects not being randomised were evidence of raised peripheral blood or sputum eosinophil count (20 [2%] subjects) and lack of compliance of completion of the eDiary (24 [3%] subjects).

Table 14 Disposition of Subjects (DREAM, ITT Population)

		Mepolizumab Dose			
	Placebo N=155 n (%)	**75 mg N=153 n (%)**	**250 mg N=152 n (%)**	**750 mg N=156 n (%)**	**Total N=616 n (%)**
Completion status					
Completed	127 (82)	129 (84)	131 (86)	133 (85)	520 (84)
Withdrawn	28 (18)	24 (16)	21 (14)	23 (15)	96 (16)
Adverse events[a]	6 (4)	5 (3)	8 (5)	9 (6)	28 (5)
Adverse event[b]	5 (3)	4 (3)	7 (5)	8 (5)	24 (4)
Lab Abnormality[c]	1 (<1)	1 (<1)	1 (<1)	1 (<1)	4 (<1)
Lack of efficacy	8 (5)	6 (4)	4 (3)	4 (3)	22 (4)
Protocol deviation	1 (<1)	1 (<1)	0	0	2 (<1)
Lost to follow-up	1 (<1)	1 (<1)	4 (3)	0	6 (<1)
Investigator discretion	1 (<1)	3 (2)	3 (2)	3 (2)	10 (2)
Withdrew consent	11 (7)	8 (5)	2 (1)	7 (4)	28 (5)
Entered follow-up phase[d]	134 (86)	133 (87)	135 (89)	137 (88)	539 (88)
Entered post follow-up phase[e]	126 (81)	130 (85)	128 (84)	129 (83)	513 (83)

a. Subjects with an adverse event leading to permanent discontinuation of investigations product or withdrawal from study.
b. Subjects with 'Adverse event' as primary reason for withdrawal.
c. Subjects with 'Subject reached protocol-defining stopping criteria' as primary reason for withdrawal and 'lab abnormality' as secondary reason for withdrawal.
d. Subjects who attended the Follow-Up (Week 56) visit.
e. Subjects who attended the Immunogenicity (Week 72) visit.

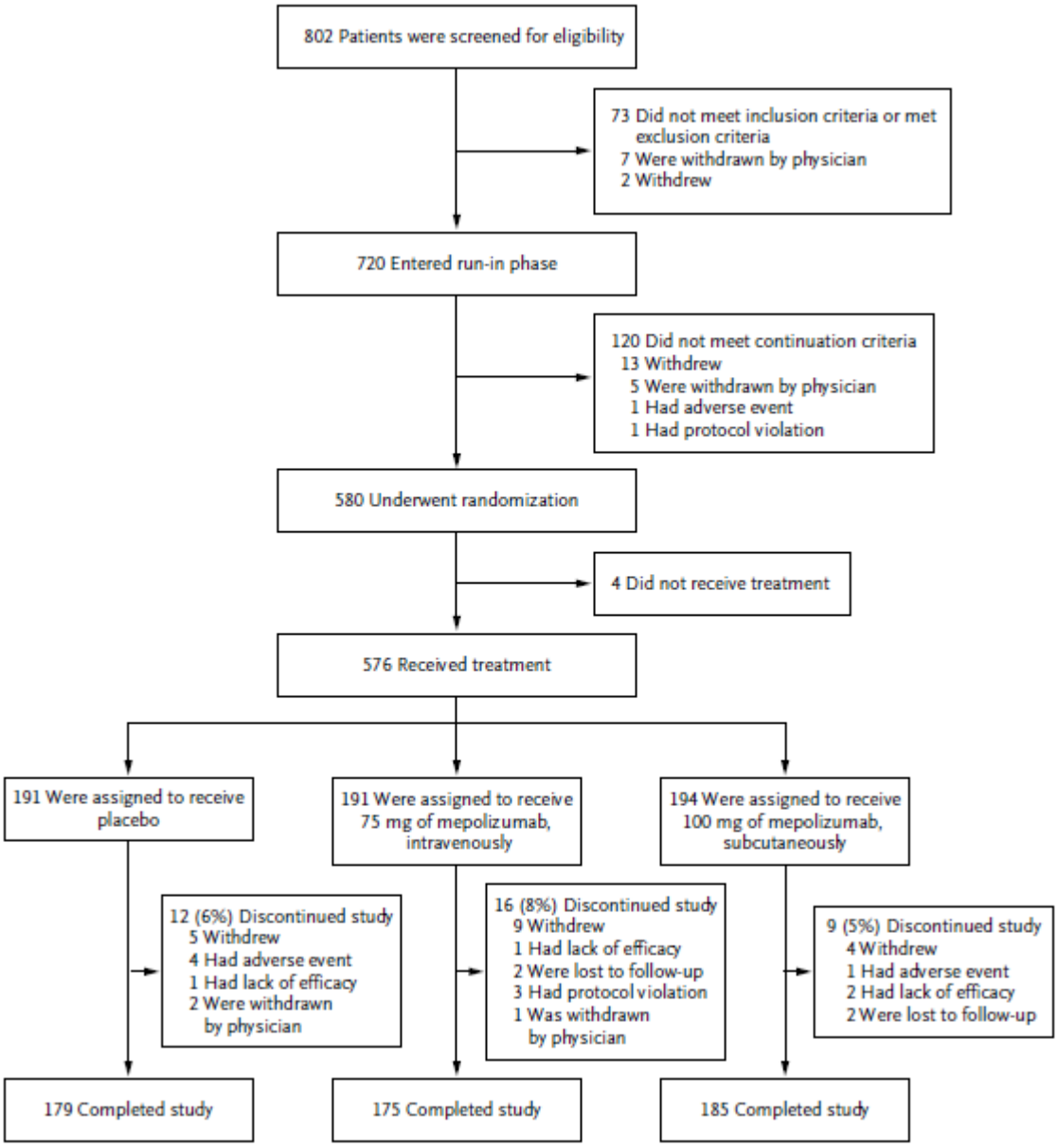
Ninety-six (16%) subjects in the ITT population withdrew from the study (Table 14). The most frequent reason for withdrawal was withdrawal of consent (28 [5%] subjects). Similar numbers of subjects in each group completed the study.

In summary, 888 subjects were included in the All Subjects Enrolled Population and 616 subjects in the ITT Population.

4.5.1.2 MENSA

In MENSA a total of 802 subjects were enrolled, 82 subjects (10%) were withdrawn at screening because they did not meet entry criteria. An additional 140 (17%) subjects were withdrawn during run-in, primarily for not meeting the continuation criteria (120/140 subjects). This has been summarised in Figure 5 below.

Figure 5 Trial profile consort diagram (MENSA)



A total of 576 subjects were randomised, received at least one dose of study drug, and were included in the ITT Population (Table 15). Four subjects were randomised but did not receive any study medication and are therefore not included in the ITT population: 2 subjects were randomised in error and 2 subjects were withdrawn due to issues in obtaining an IV line.

Table 15 Disposition of Subjects (MENSA, ITT Population)

Status	Number (%) of Subjects			
	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194	Total N=576
Completed	179 (94)	175 (92)	185 (95)	539 (94)
Withdrawn[1]	12 (6)	16 (8)	9 (5)	37 (6)
Entered open-label extension study[2]	175 (90)	171 (90)	176 (91)	522 (91)
Primary reason for withdrawal[3]				
Withdrawal by subject	5 (3)	9 (5)	4 (2)	18 (3)
Adverse event[4]	4 (2)	0	1 (<1)	5 (<1)
Lack of efficacy	1 (<1)	1 (<1)	2 (1)	4 (<1)
Lost to Follow-up	0	2 (1)	2 (1)	4 (<1)
Protocol deviation	0	3 (2)	0	3 (<1)
Physician decision	2 (1)	1 (<1)	0	3 (<1)

1. Four subjects were randomised and withdrawn without receiving any study medication and are not in the ITT Population.
2. COSMOS study
3. Only one primary reason for withdrawal was recorded.
4. Subjects with an adverse event leading to permanent discontinuation of study drug or withdrawal from study.

The majority of subjects in the ITT Population completed the study (539, 94%) and 522 subjects continued treatment in the OLE study COSMOS (91%). Thirty-seven subjects (12 in the placebo group and 16 and 9 subjects in the mepolizumab 75 mg IV and 100 mg SC groups, respectively) withdrew from the study prematurely. The main reason for withdrawal was voluntary withdrawal (18 subjects [3%]), followed by adverse events (5 subjects [<1%]).

4.5.1.3 SIRIUS

In SIRIUS a total of 185 subjects were screened for this study; 3 subjects were withdrawn at screening because they did not meet the entry criteria. An additional 47 subjects were withdrawn during run-in (OCS Optimisation Phase), primarily for not meeting the continuation/randomisation criteria (42/47 subjects). The majority of these Run-in Failures (27 subjects) did not achieve an optimised OCS dose (17 subjects) or failed to meet the eosinophilic phenotype as defined in the protocol (10 subjects). This has been summarised in Figure 6.

Figure 6 Trial profile consort diagram (SIRIUS)

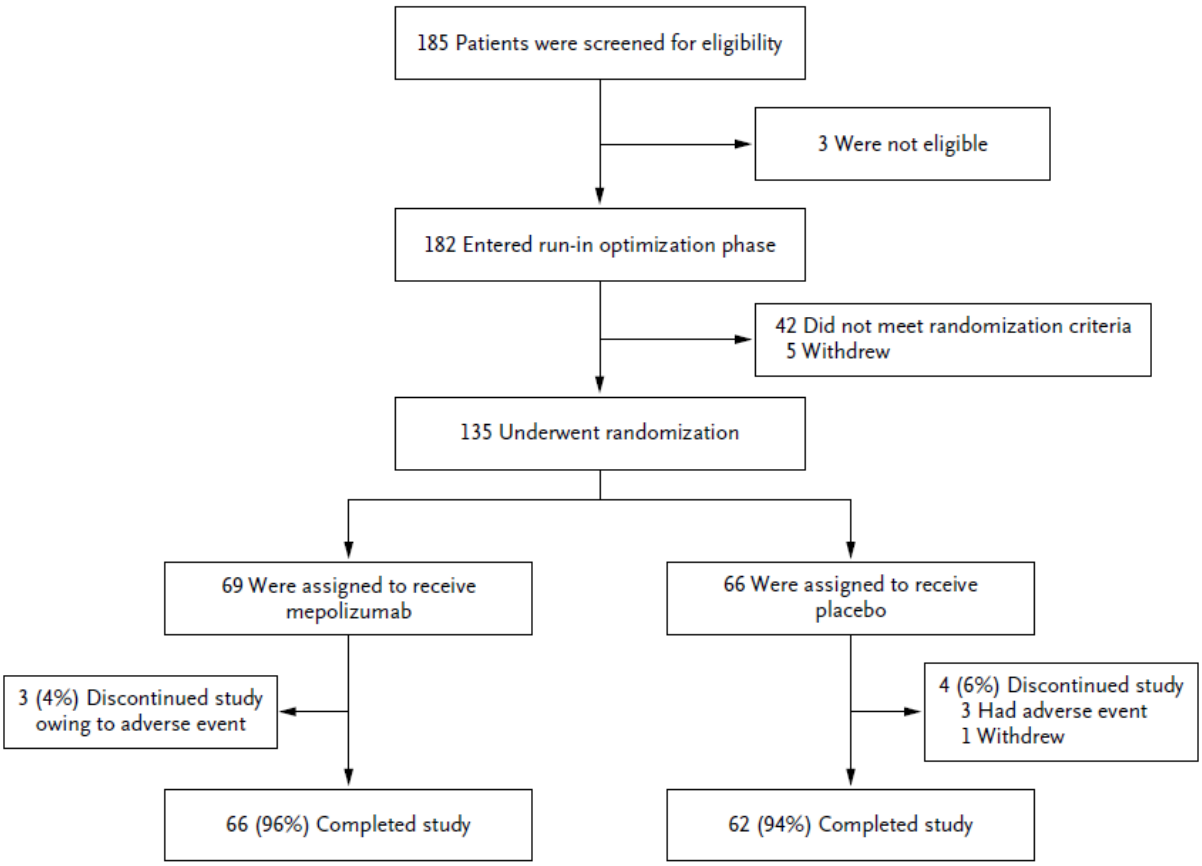


Table 16 Disposition of subjects (SIRIUS, ITT Population)

Status	Number (%) of Subjects		
	Placebo N=66	Mepolizumab 100 mg SC N=69	Total N=135
Completed	62 (94)	66 (96)	128 (95)
Withdrawn	4 (6)	3 (4)	7 (5)
Entered open-label extension study[1,2]	61 (92)	65 (94)	126 (93)
Primary reason for withdrawal[3]			
Adverse event	3 (5)	3 (4)	6 (4)
Subject withdrew	1 (2)	0	1 (<1)

1. Study MEA115661
2. Two subjects (Subject 341 and Subject 344) elected not to continue in the OLE study.
3. Only one primary reason for withdrawal was recorded.

A total of 135 subjects were randomised, received at least one dose of study drug, and were included in the ITT Population. The majority of subjects in the ITT Population completed the study (95%) and continued treatment in the OLE study COSMOS (93%). Seven subjects (4 in the placebo group and 3 in the mepolizumab group) withdrew from the study prematurely. All subjects withdrew due to AEs except one in the placebo group, who voluntarily withdrew from the study (Table 16).

4.5.2 Patient demographics and baseline characteristics

The demographics and baseline characteristics of patients recruited for DREAM and MENSA were similar and there were no notable differences between the treatment groups within each study for the ITT populations. The population was representative of patients who had severe asthma with eosinophilic inflammation. A meta-analysis of both DREAM and MENSA's demographics and baseline characteristics can be found in section 4.9 and in Appendix 8.3.

In DREAM, subjects entering the study had a mean (range) age of 48.6 (15–74) years; 229 (37%) subjects were male and 387 (63%) subjects were female. The proportion of adolescents enrolled in the study was small. Most subjects were white (554 [90%]). Mean body mass index (BMI) was 28.5 kg/m2, indicating subjects tended to be overweight.

In MENSA, the study population was primarily white (78%) and more than half were female (57%); the mean age was 50 years. Twenty-five adolescent subjects (9 in each of the placebo and mepolizumab 75 mg IV groups and 7 in the mepolizumab 100 mg SC group) and 80 elderly subjects (26 in the placebo group, 24 in the mepolizumab 75 mg IV group and 30 in the mepolizumab 100 mg SC group) participated in the study. Subjects of Hispanic/Latino ethnicity comprised 51 (9%) of the ITT Population. Mean BMI was 27.77 kg/m^2, indicating subjects tended to be overweight.

Patients enrolled in both the exacerbation studies had a long duration of asthma with a mean of at least 19 years; half of the patients were atopic. The mean baseline blood eosinophil was 250 cells/μL in DREAM and 290 cells/μL in MENSA. Despite being treated with high dose ICS plus an additional maintenance treatment(s) (and 27% with daily OCS), patients had a history of frequent exacerbations with a mean of 3.6 per year in both studies. In DREAM 44% of patients required an ED visit or hospitalisation due to an exacerbation in the previous year, compared to 33% in MENSA. The baseline ACQ scores (2.2 and 2.4) were greater than the threshold of 1.5 for defining uncontrolled disease. A summary of this can be found in Appendix 8.3.

There were 188 subjects (30.5%, DREAM) and 139 subjects (24%, MENSA) that were on baseline maintenance OCS. The baseline maintenance OCS dose between the two studies also had a slight difference as the mean average dose for the total ITT Population was 17.4mg for DREAM and 13.2mg for MENSA. A table showing baseline OCS dose for both DREAM and MENSA can be found in Appendix 8.3.

Demography and baseline characteristics of patients in SIRIUS were consistent with the population in the exacerbation studies. Demography was comparable between the treatment groups, except for a larger proportion of females in the mepolizumab group (64%) compared with the placebo group (45%). The patients in this study were primarily white (95%), more than half were female (55%), the mean age was 50 years, and patients had an elevated BMI (28.7 kg/m2) indicating they were also overweight. The mean average optimised baseline dose of OCS was just short of 13mg. A table showing a summary of the demographic characteristics has been included in Appendix 8.3.

Nearly half of the patients in this study had been taking OCS for more than 5 years; median daily OCS doses at screening were 15.0 mg in the placebo group and 12.5 mg in the mepolizumab group. After the Optimisation Phase, median daily OCS doses were adjusted to 12.5 mg and 10 mg (i.e., Baseline doses), respectively. A summary of OCS history and daily dose for SIRIUS has been provided in Appendix 8.3.

4.5.3 GSK proposed population

For both the MENSA and SIRIUS studies, subgroup demographic data was collected as shown in Table 17 and Table 18 below. For MENSA there were two subgroups: 1) Subjects with ≥150 cells/μL baseline blood eosinophils and ≥4 exacerbations in past year or baseline maintenance OCS use with <4 exacerbations in the previous year (GSK proposed population) and 2) ≥150 cells/μL baseline blood eosinophils and ≥4 exacerbations in past year (GSK Proposed Population excluding mOCS users with <4 exacerbations in the previous year). The SIRIUS subgroup consisted of subjects with ≥150 cells/μL baseline blood eosinophils, no further criteria were required as all subjects in the study were on maintenance OCS therapy (with more or less than 4 exacerbations). This also represented the GSK Proposed Population. Data from the subgroups were compared with the ITT populations (see Section 4.7 for the rationale for the subgroups). No subgroup analyses were performed for DREAM.

Table 17 Summary of Demographic Characteristics, GSK proposed population (MENSA)

		GSK Proposed Population excluding mOCS users with <4 exacerbations				GSK Proposed Population			
Characteristic	Analysis	Placebo	Mepo 75mg IV	Mepo 100mg	Total	Placebo	Mepo 75mg IV	Mepo 100mg	Total
Age (yrs)	n	45	48	54	147	64	65	78	207
	Mean (SD)	47.3 (14.88)	51.8 (14.05)	53.7 (12.59)	51.1 (13.96)	48 (14.19)	50.8 (14.64)	53.1 (12.31)	50.8 (13.76)
	Median(Min, Max)	50 (12, 69)	53.5 (17, 82)	55.5 (16, 77)	53 (12, 82)	49 (12, 73)	52 (15, 82)	53 (16, 77)	52 (12, 82)
Sex	n	45	48	54	147	64	65	78	207
	Female	23 (51%)	27 (56%)	34 (63%)	84 (57%)	33 (52%)	37 (57%)	47 (60%)	117 (57%)
Ethnicity	n	45	48	54	147	64	65	78	207
	Hispanic or Latino	1 (2%)	4 (8%)	3 (6%)	8 (5%)	2 (3%)	6 (9%)	3 (4%)	11 (5%)
	Not Hispanic or Latino	44 (98)	44 (92%)	51 (94%)	139 (95%)	62 (97%)	59 (91%)	75 (96%)	196 (95%)
Weight (kg)	n	45	48	54	147	64	65	78	207
	Mean (SD)	76.2 (19.36)	77.09 (16.418)	77.43 (23.482)	76.94 (20.004)	77.76 (20.718)	75.6 (16.851)	75.78 (21.027)	76.33 (19.638)
	Min.	45	45	45	45	45	45	45	45
	Max.	132	105.4	140	140	138	105.4	140	140
Duration of Asthma	n	45	48	54	147	64	65	78	207
	≥1 to <5 years	8 (18%)	8 (17%)	2 (4%)	18 (12%)	9 (14%)	12 (18%)	5 (6%)	26 (13%)
	≥5 to <10 years	7 (16%)	10 (21%)	9 (17%)	26 (18%)	10 (16%)	11 (17%)	13 (17%)	34 (16%)
	≥10 to <15 years	7 (16%)	7 (15%)	15 (28%)	29 (20%)	10 (16%)	11 (17%)	17 (22%)	38 (18%)
	≥15 to <20 years	6 (13%)	5 (10%)	4 (7%)	15 (10%)	9 (14%)	7 (11%)	5 (6%)	21 (10%)
	≥20 to <25 years	3 (7%)	6 (13%)	8 (15%)	17 (12%)	4 (6%)	6 (9%)	11 (14%)	21 (10%)
	≥25 years	14 (31%)	12 (25%)	16 (30%)	42 (29%)	22 (34%)	18 (28%)	27 (35%)	67 (32%)
	Mean (SD)	18.7 (15.02)	17.6 (14.05)	19.6 (11.97)	18.7 (13.57)	19.9 (15.38)	17.8 (14.43)	20.7 (13.05)	19.6 (14.22)
	Median (Min, Max)	15 (1, 57)	13 (1, 56)	17.5 (3, 49)	15 (1, 57)	15 (1, 60)	13 (1, 56)	18.5 (2, 51)	15 (1, 60)
Airway Inflammation Characteristics:			:						
At visit 1 elevated peripheral blood eosinophil count ≥150 cells/µL	Yes	41 (91%)	46 (96%)	45 (83%)	132 (90%)	59 (92%)	62 (95%)	67 (86%)	188 (91%)
	No	4 (9%)	2 (4%)	7 (13%)	13 (9%)	5 (8%)	2 (3%)	9 (12%)	16 (8%)
	Missing	0	0	2 (4%)	2 (1%)	0	1 (2%)	2 (3%)	3 (1%)
Baseline OCS daily dose (prednisolone equivalent) [2]	n	14	14	13	41	33	29	37	99
	<7.5 mg/day	4 (29%)	6 (43%)	5 (38%)	15 (37%)	13 (39%)	14 (48%)	18 (49%)	45 (45%)
	≥7.5-<15 mg/day	5 (36%)	3 (21%)	4 (31%)	12 (29%)	11 (33%)	8 (28%)	8 (22%)	27 (27%)
	≥15-<30 mg/day	3 (21%)	2 (14%)	2 (15%)	7 (17%)	5 (15%)	3 (10)	7 (19%)	15 (15%)
	≥30 mg/day	2 (14%)	3 (21%)	2 (15%)	7 (17%)	4 (12%)	4 (14%)	4 (11%)	12 (12%)
	Mean (SD)	17.5 (19.69)	13.6 (11.88)	14.3 (12.61)	15.1 (14.92)	14.6 (15.73)	11.3 (9.89)	11.9 (10.82)	12.6 (12.4)
	Median (Min, Max)	10 (5, 80)	8.7 (3, 40)	10 (2, 40)	10 (2, 80)	10 (5, 80)	7.5 (1, 40)	7.5 (2, 40)	10 (1, 80)
Total number of exacerbations	n	45	48	54	147	64	65	78	207
	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	12 (19%)	8 (12%)	15 (19%)	35 (17%)
	3	0	0	0	0	7 (11%)	9 (14%)	9 (12%)	25 (12%)
	4	19 (42%)	21 (44%)	22 (41%)	62 (42%)	19 (30%)	21 (32%)	22 (28%)	62 (30%)
	>4	26 (58%)	27 (56%)	32 (59%)	85 (58%)	26 (41%)	27 (42%)	32 (41%)	85 (41%)
	Mean (SD)	6.5 (3.74)	5.9 (2.49)	6.1 (3.29)	6.2 (3.19)	5.3 (3.67)	5 (2.61)	5 (3.25)	5.1 (3.19)

	Median (Min, Max)	5 (4, 19)	5 (4, 14)	5(4, 21)	5(4, 21)	4(2, 19)	4(2, 14)	4(2, 21)	4 (2, 21)
Total number of exacerbations that required ER visits and/or hospitalisation	n	45	48	54	147	64	65	78	207
	0	20 (44%)	23 (48%)	34 (63%)	77 (52%)	32 (50%)	31 (48%)	53 (68%)	116 (56%)
	1	7 (16%)	10 (21%)	6 (11%)	23 (16%)	13 (20%)	17 (26%)	11 (14%)	41 (20%)
	2	8 (18%)	7 (15%)	3 (6%)	18 (12%)	8 (13%)	9 (14%)	3 (4%)	20 (10%)
	3	3 (7%)	5 (10%)	3 (6%)	11 (7%)	4 (6%)	5 (8%)	3 (4%)	12 (6%)
	4	1 (2%)	1 (2%)	4 (7%)	6 (4%)	1 (2%)	1 (2%)	4 (5%)	6 (3%)
	>4	6 (13%)	2 (4%)	4 (7%)	12 (8%)	6 (9%)	2 (3%)	4 (5%)	12 (6%)
Total number of exacerbations that required hospitalisation	n	45	48	54	147	64	65	78	207
	0	27 (60%)	32 (67%)	39 (72%)	98 (67%)	43 (67%)	42 (65%)	60 (77%)	145 (70%)
	1	8 (18%)	10 (21%)	6 (11%)	24 (16%)	10 (16%)	16 (25%)	9 (12%)	35 (17%)
	2	3 (7%)	5 (10%)	4 (7%)	12 (8%)	3 (5%)	6 (9%)	4 (5%)	13 (6%)
	3	4 (9%)	1 (2%)	4 (7%)	9 (6%)	5 (8%)	1 (2%)	4 (5%)	10 (5%)
	4	1 (2%)	0	1 (2%)	2 (1%)	1 (2%)	0	1 (1%)	2 (<1%)
	>4	2 (4%)	0	0	2 (1%)	2 (3%)	0	0	2 (<1%)
Previously Administered Xolair:	n	45	48	54	147	64	65	78	207
	Yes	9 (20%)	9 (19%)	9 (17%)	27 (18%)	11 (17%)	15 (23%)	16 (21%)	42 (20%)
	No	36 (80%)	39 (81%)	45 (83%)	120 (82%)	53 (83%)	50 (77%)	62 (79%)	165 (80%)
Previously Failed on Xolair:	n	9	9	9	27	11	15	16	42
	Yes	9 (100%)	8 (89%)	8 (89%)	25 (93%)	11 (100%)	13 (87%)	15 (94%)	39 (93%)
	No	0	1 (11%)	1 (11%)	2 (7%)	0	2 (13%)	1 (6%)	3 (7%)
Baseline:									
Pre-bronchodilator % Predicted Normal FEV_1 (%)	n	45	48	54	147	64	65	78	207
	Mean (SD)	60.2 (18.92)	61.9 (21.32)	58.2 (17.68)	60 (19.24)	59.2 (18.85)	60 (21.01)	57.5 (17.51)	58.8 (19.01)
	Median (Min, Max)	55.8 (33, 109)	63.1 (24, 128)	61.7 (30, 98)	60.9 (24, 128)	56.2 (18, 109)	62.9 (24, 128)	57.1 (30, 98)	57.7 (18, 128)
Pre-bronchodilator FEV_1/FVC	n	45	48	54	147	64	65	78	207
	Mean (SD)	0.64 (0.134)	0.64 (0.133)	0.64 (0.135)	0.64 (0.133)	0.62 (0.137)	0.62 (0.137)	0.63 (0.13)	0.62 (0.134)
	Median (Min, Max)	0.63 (0.4, 1)	0.64 (0.3, 0.9)	0.64 (0.3, 0.9)	0.63 (0.3, 1)	0.62 (0.4, 1)	0.63 (0.3, 0.9)	0.63 (0.3, 0.9)	0.63 (0.3, 1)
Baseline Blood Eosinophils (cells/µL)	n	45	48	54		64	65	78	
	Geo. Mean	480	440	510		460	460	480	
	Median (Min, Max)	450 (200, 3000)	420 (200, 1900)	510 (200, 2100)		430 (200, 3000)	430 (200, 2200)	460 (200, 2200)	
Baseline Total IgE (U/mL)	n	44	44	51		61	61	71	
	Geo. Mean	154.54	220.6	155.26		125.47	193.41	148.04	
	Median (Min, Max)	132.5 (3, 11220)	204.5 (7, 4880)	188 (10, 1571)		144 (2, 11220)	173 (7, 4880)	192 (1, 1571)	
Baseline ACQ-5 Mean Score	n	45	48	53		64	65	76	
	Mean (SD)	2.49 (1.425)	2.25 (1.071)	2.36 (1.13)		2.39 (1.323)	2.28 (1.088)	2.46 (1.181)	
	Median (Min, Max)	2.6 (0, 5.8)	2.3 (0.2, 4.2)	2.2 (0, 5.2)		2.5 (0, 5.8)	2.4 (0, 4.8)	2.3 (0, 5.2)	
Baseline SGRQ Total Score	n	45	48	54		64	65	77	
	Mean (SD)	52.2 (20.67)	47.5 (18.48)	51.8 (19.11)		50.2 (19.91)	48.7 (18.9)	50.9 (19.49)	
	Median (Min, Max)	51.4 (15, 95)	51.7 (6, 78)	50.1 (17, 90)		49.6 (15, 95)	51.6 (5, 82)	50.1 (7, 90)	

Table 18 Summary of Demographic Characteristics, Subjects with ≥150 cells/µL Baseline Blood Eosinophils (SIRIUS)

Characteristic		GSK Proposed Population		
		Placebo (n=48)	Mepolizumab 100mg SC (n=54)	Total (n=102)
Age (yrs)	n	48	54	102
	Mean	49.2	50	49.6
	SD	9.92	14.53	12.52
	Median	51	52	51
	Min.	28	16	16
	Max.	69	74	74
Sex	n	48	54	102
	Female	23 (48%)	37 (69%)	60 (59%)
Ethnicity	n	48	54	102
	Hispanic or Latino	3 (6%)	2 (4%)	5 (5%)
	Not Hispanic or Latino	45 (94%)	52 (96%)	97 (95%)
Weight (kg)	n	48	54	102
	Mean	86.06	77.57	81.56
	SD	20.158	16.926	18.909
	Min.	55	47	47
	Max.	131.5	125	131.5
Duration of Asthma	n	48	54	102
	≥1 to <5 years	7 (15%)	5 (9%)	12 (12%)
	≥5 to <10 years	7 (15%)	12 (22%)	19 (19%)
	≥10 to <15 years	6 (13%)	5 (9%)	11 (11%)
	≥15 to <20 years	8 (17%)	9 (17%)	17 (17%)
	≥20 to <25 years	4 (8%)	8 (15%)	12 (12%)
	≥25 years	16 (33%)	15 (28%)	31 (30%)
	Mean	19.6	17.4	18.4
	SD	13.92	11.44	12.65
	Median	17.5	15	16
	Min.	2	2	2
	Max.	58	55	58
Airway Inflammation Characteristics: Between visit 1 and visit 3 elevated peripheral blood eosinophil count ≥150/µL	n	48 48 (100%)	54 54 (100%)	102 102 (100%)
Baseline OCS daily dose (prednisolone equivalent):	n	48	54	102
	5-<10 mg/day	16 (33%)	19 (35%)	35 (34%)
	10-<15 mg/day	18 (38%)	21 (39%)	39 (38%)
	≥15 mg/day	14 (29%)	14 (26%)	28 (27%)
	Mean	11.7	12.1	11.9
	SD	4.93	7.3	6.27
	Median	10	10	10
	Min.	5	5	5
	Max.	25	35	35
Duration of OCS use:	n	48	54	102
	<5 years	26 (54%)	26 (48%)	52 (51%)
	≥5 years	22 (46%)	28 (52%)	50 (49%)
Total number of exacerbations	n	48	54	102
	0	6 (13%)	11 (20%)	17 (17%)
	1	10 (21%)	10 (19%)	20 (20%)
	2	8 (17%)	3 (6%)	11 (11%)
	3	9 (19%)	8 (15%)	17 (17%)
	4	7 (15%)	12 (22%)	19 (19%)

	>4	8 (17%)	10 (19%)	18 (18%)
	Mean	3	3.3	3.2
	SD	2.78	3.54	3.19
	Median	2.5	3	3
	Min.	0	0	0
	Max.	13	16	16
Total number of exacerbations that required ER visits and/or hospitalisation	n	48	54	102
	0	41 (85%)	36 (67%)	77 (75%)
	1	3 (6%)	9 (17%)	12 (12%)
	2	1 (2%)	4 (7%)	5 (5%)
	3	1 (2%)	2 (4%)	3 (3%)
	4	2 (4%)	1 (2%)	3 (3%)
	>4	0	2 (4%)	2 (2%)
Total number of exacerbations that required hospitalisation	n	48	54	102
	0	41 (85%)	43 (80%)	84 (82%)
	1	4 (8%)	6 (11%)	10 (10%)
	2	0	3 (6%)	3 (3%)
	3	2 (4%)	1 (2%)	3 (3%)
	4	1 (2%)	1 (2%)	2 (2%)
	>4	0	0	0
Previously Administered Xolair:	n	48	54	102
	Yes	18 (38%)	19 (35%)	37 (36%)
	No	30 (63%)	35 (65%)	65 (64%)
Previously Failed on Xolair:	n	18	19	37
	Yes	18 (100%)	19 (100%)	37 (100%)
	No	0	0	0
Pre-bronchodilator % Predicted Normal FEV_1 (%)	n	48	54	102
	Mean	55.8	57.8	56.9
	SD	17.51	16.52	16.94
	Median	57.8	59.4	58.7
	Min.	15	18	15
	Max.	93	94	94
Pre-bronchodilator FEV_1/FVC	n	48	54	102
	Mean	0.6	0.62	0.61
	SD	0.108	0.114	0.111
	Median	0.61	0.61	0.61
	Min.	0.3	0.3	0.3
	Max.	0.8	0.9	0.9
Baseline Blood Eosinophils (cells/µL)	n	48	54	
	Geo. Mean	370	420	
	Median	400	400	
	Min.	200	200	
	Max.	1800	2300	
Baseline Total IgE (U/mL)	n	44	49	
	Geo. Mean	103.36	114.26	
	Median	101	106	
	Min.	1	3	
	Max.	3445	1487	
Baseline ACQ-5 Mean Score	n	48	54	
	Mean	2.06	2.16	
	SD	1.172	1.162	
	Median	2	2.2	
	Min.	0.2	0	
	Max.	4.8	4.4	
Baseline SGRQ Total Score	n	48	54	
	Mean	43.6	50.1	
	SD	17.38	16.3	
	Median	41.9	52.1	
	Min.	8	18	
	Max.	77	84	
Screening Dose (Visit	n	48	54	102

1)	>35mg	0	0	0
	>30 - 35mg	1 (2%)	3 (6%)	4 (4%)
	>25 - 30mg	2 (4%)	5 (9%)	7 (7%)
	>20 - 25mg	1 (2%)	3 (6%)	4 (4%)
	>15 - 20mg	13 (27%)	11 (20%)	24 (24%)
	>12.5 - 15mg	5 (10%)	6 (11%)	11 (11%)
	>10.0 - 12.5g	5 (10%)	2 (4%)	7 (7%)
	>7.5 - 10mg	15 (31%)	8 (15%)	23 (23%)
	>5.0 - 7.5mg	3 (6%)	6 (11%)	9 (9%)
	5mg	3 (6%)	10 (19%)	13 (13%)
	0 - <5.0mg	0	0	0
	Mean	14.5	15.6	15.1
	SD	6.67	9.15	8.05
	Median	12.5	15	12.5
	Min	5	5	5
	Max	35	35	35
Optimised (baseline) dose	n	48	54	102
	>35mg	0	0	0
	>30 - 35mg	0	2 (4%)	2 (2%)
	>25 - 30mg	0	2 (4%)	2 (2%)
	>20 - 25mg	1 (2%)	1 (2%)	2 (2%)
	>15 - 20mg	7 (15%)	3 (6%)	10 (10%)
	>12.5 - 15mg	6 (13%)	6 (11%)	12 (12%)
	>10.0 - 12.5g	8 (17%)	7 (13%)	15 (15%)
	>7.5 - 10mg	10 (21%)	14 (26%)	24 (24%)
	>5.0 - 7.5mg	11 (23%)	10 (19%)	21 (21%)
	5mg	5 (10%)	9 (17%)	14 (14%)
	0 - <5.0mg	0	0	0
	Mean	11.7	12.1	11.9
	SD	4.93	7.3	6.27
	Median	10	10	10
	Min	5	5	5
	Max	25	35	35

Comparison of GSK proposed to ITT population demographics

The majority of data is comparable with the ITT population. However, there are a few noticeable differences. An increase in baseline rate of exacerbations in the previous 12 months both in the GSK proposed population (5.1/year) and the GSK proposed population excluding mOCS users with <4 exacerbations (6.2/year) was observed in MENSA (ITT 3.6/year). In SIRIUS, baseline exacerbation rate in the past year remained stable between the ITT and GSK proposed population (3.1/year vs. 3.3/year, respectively). There was a considerable difference in the baseline blood eosinophils, where in MENSA the GSK proposed population and the GSK population excluding mOCS users with <4 exacerbations had total averages of 460 to 510 cells/μL, whereas the ITT Population had an average of 290 to 320 cells/μL. In SIRIUS, there was also a considerable difference in the baseline blood eosinophil count; in the GSK proposed population 370 to 420 cells/μL, compared to the ITT population of 230 to 250 cells/μL. The higher baseline eosinophil count along with the exacerbation rate seen in the GSK proposed populations versus the ITT populations, demonstrated that the selection criteria have identified a more severe refractory eosinophilic asthma population of the clinical trial population.

Other than the demographic differences discussed above, the tables above (Table 17, Table 18) show that the rest of the GSK proposed populations were consistent with the ITT Population.

Comparison of treatment arms within GSK proposed and ITT population demographics

When comparing the treatment arms within the MENSA subgroups, these were reasonably consistent in the GSK proposed population. There was a slight difference across the treatment arms by gender, as placebo, mepolizumab 75mg IV and mepolizumab 100mg SC had 52%, 57% and 60% females, respectively (GSK proposed population excluding mOCS users with <4 exacerbations, 51%, 56%, 63%). The baseline OCS daily dose also had slight variations as the mean across treatment arms was 14.6mg, 11.3mg and 11.9mg in the placebo, mepolizumab 75mg IV and mepolizumab 100 SC arms, respectively (GSK proposed population excluding mOCS users with <4 exacerbations 17.5mg, 13.6mg, 14.3mg). A similar trend was observed in the ITT population (15.1mg, 12mg, and 12.6mg, respectively). All other characteristics were relatively consistent between the two MENSA subgroups in the GSK proposed population and ITT populations.

The GSK proposed and ITT populations from the SIRIUS trial, also showed relative consistency within the treatment arms. Slight differences could be seen in gender, as in the GSK proposed population there were 48% females in the placebo arm, and 69% in the mepolizumab 100mg SC arm (ITT population 45%, 64%, respectively). There was also a difference in weight as the treatment arms had a mean average of 86.06kg and 77.57kg (ITT 87.46kg and 79.36kg) in the placebo and mepolizumab 100mg SC arms, respectively. The duration of asthma varied slightly with the placebo arm having a mean 19.6 years, and the mepolizumab 100mg SC arm 17.4 years (ITT 20.1 years and 17.4 years, respectively). All other characteristics were relatively consistent.

4.6 Quality assessment of the relevant randomised controlled trials

4.6.1 Quality assessment of RCTs

A quality assessment of the relevant RCTs is provided in Table 19

Table 19 Quality assessment results for parallel group RCTs.

Trial number	DREAM	MENSA	SIRIUS
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

For all three studies, the study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational centre ethics committee or Institutional Review Board (IRB), in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) and applicable country-specific requirements, including US 21 Code of Federal Regulations (CFR) 312.3(b) for constitution of IECs. These studies were conducted in accordance with ICH GCP and all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008. Investigators were trained to conduct the study in accordance with GCP and the study protocol as defined in ICH E3, Section 9.6. Written commitments were obtained from investigators to comply with GCP and to conduct the study in accordance with the protocol.

Written informed consent was obtained from each subject prior to the performance of any study-specific procedures. Electronic case report forms (eCRFs) were provided for each subject's data to be recorded. Subjects were assigned to study treatment in accordance with the randomisation schedule which was generated using the GSK validated randomisation software RandAll.

Once prepared mepolizumab and placebo were identical in appearance and were administered by a designated blinded member of the site staff. Investigational product was prepared by a designated unblinded person, independent of the study assessments. The blindness of those involved in the evaluation of the study i.e., physician/nurse and subject was maintained at all times.

A subject was regarded as having completed the study if he/she completed all phases of the study (screening, treatment period and follow-up). Subjects may have been withdrawn from study treatment at any time by the investigator if it was considered to be detrimental for them to continue in the study. Reasons for withdrawal could have included: an AE, lost to follow-up, protocol violation, lack of efficacy, sponsor terminated study, non-compliance, pregnancy, abnormal LFT, abnormal laboratory results, or for any other reason.

Full details of study assessments and procedures can be found in the CSRs.[51,114,115]

4.6.2 Relevance to UK population

The mepolizumab clinical trial population was representative of the UK patient population with severe refractory eosinophilic asthma, looking at demographics and disease characteristics of subjects enrolled (see full list of inclusion and exclusion criteria in study CSRs). Subjects were at stage 4 and 5 of the BTS/SIGN treatment algorithm, treated on high dose inhaled corticosteroids plus an additional controller(s) (maintenance treatment[s]), with or without maintenance oral corticosteroids. Despite optimised therapy, in DREAM and MENSA, patients had to

have ≥2 exacerbations in the last year (mean baseline exacerbation rate 3.6/year for ITT both DREAM and MENSA); while in SIRIUS all patients were on maintenance OCS (mean OCS dose 12.8 mg, mean exacerbation rate ITT 3.1/year).

A subgroup of patients for whom add-on mepolizumab therapy would provide additional benefit was identified and validated by independent severe asthma specialists in advisory boards. Patients in the GSK proposed population again were representative of the UK patient population, but identified a more severe refractory eosinophilic asthma population, with a higher rate of exacerbations (MENSA, mean 5.1 vs. 3.6 ITT).

Although participation in the UK trial centres was limited due to competitive patient recruitment and the number of patients enrolled in relation to country size, there were no identified reasons why geographical regional differences would cause the results of the clinical trials to be any different in England and Wales. Therefore, the clinical benefits of mepolizumab would be applicable to eligible patients in UK clinical practice.

4.7 Clinical effectiveness results of the relevant randomised controlled trials

All p-values presented in this section are unadjusted. For the ITT population, multiplicity across treatment comparisons of the primary and secondary endpoints was controlled using a closed testing procedure in MENSA, as described in Section 4.4. Results of the step-down testing procedure for the primary and secondary endpoints for each study are provided in Appendix 8.4. For SIRIUS no adjustments for multiplicity were made because the secondary endpoint analyses were considered as sensitivity analyses to the primary endpoint.

4.7.1 European Medicines Agency (EMA) license

The EMA licensed indication for mepolizumab is as an add-on treatment for severe refractory eosinophilic asthma in adult patients (SmPC section 4.1).

4.7.2 GSK proposed population

Mindful of NHS resources GSK have identified a more severe population within the anticipated licence with increased disease burden and an enhanced potential for clinical benefit and a more cost effective use of NHS resources. The population have been identified taking into account the clinical trial population (severe refractory eosinophilic asthma patients at step 4 or 5 of the BTS/SIGN treatment algorithm), the clinical trial results presented below and clinical specialists' opinion; details of the rationale and evidence for this is given below:

Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/μl at initiation of treatment; and ≥4 exacerbations in the previous year or dependency on systemic corticosteroids (maintenance OCS).

GSK are seeking a recommendation in this targeted population and therefore this will be the primary focus of this section although for completeness we will also present the results from the ITT population.

4.7.3 Rational for the GSK proposed population

4.7.3.1 Identified responder patient population from clinical trials

The proposed patient population for mepolizumab is based on key learnings from studies in the clinical development program. Based on the positive Proof-of-Concept study results in severe refractory asthma patients (patients on high dose ICS plus additional maintenance treatment[s] and ≥2 exacerbations), DREAM was conducted to evaluate the efficacy and safety of 75 mg, 250 mg, and 750 mg IV doses of mepolizumab compared with placebo in addition to standard of care for 52 weeks. Both Proof-of-Concept studies were conducted at specialised centres and evidence of eosinophilic inflammation was documented through collection of induced sputum, a procedure performed at these centres. Since collection of sputum eosinophils is difficult and not routinely performed in clinical practice, DREAM used an expanded set of four criteria to identify the presence of eosinophilic inflammation (see section 4.3). DREAM confirmed that mepolizumab produced clinically important reductions in clinically significant exacerbations that were not dose dependent (section 4.7.5 and 4.9 for results).

Further modelling and subgroup analyses were performed in order to understand the groups of patients for which mepolizumab was most effective in reducing exacerbations. Modelling analyses investigated various clinical characteristics as individual covariates in DREAM (i.e. gender, age, weight, geographical region, baseline % predicted FEV_1, reversibility at screening, number of exacerbations in previous year, baseline blood eosinophil count, baseline use of maintenance OCS, and IgE level) to distinguish which variables would best predict a reduction in the rate of exacerbations. The model identified blood eosinophils as the strongest predictor of treatment response. In addition, blood eosinophils are part of a full blood count, a test routinely performed in current clinical practice in severe asthma patients and thus would be easy to implement as it does not add additional cost or service requirements, unlike other markers such as sputum eosinophil count and IgE concentration.

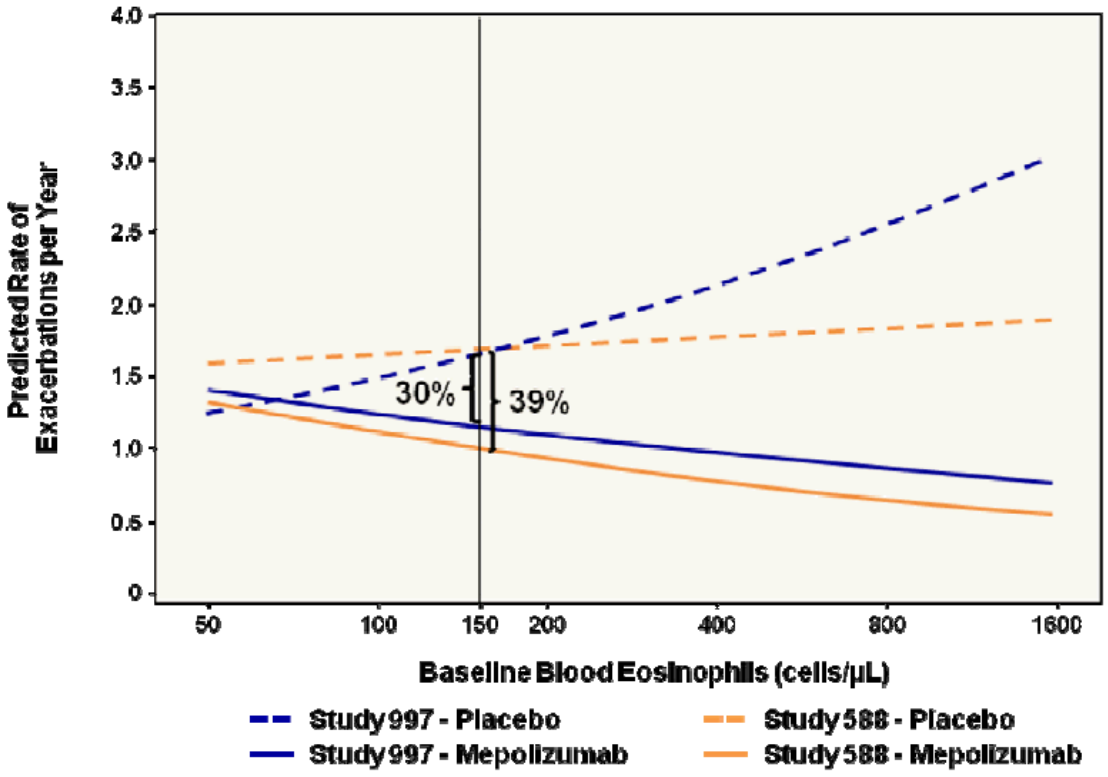
Based on available literature regarding add-on therapies in asthma, which showed a 20 to 25% reduction in exacerbations as clinically relevant, GSK applied a reduction in the rate of exacerbations of at least 30% to represent a clinically meaningful benefit in patients with severe asthma who are uncontrolled on maximal standard of care therapy[58,61,116]

The EMA have considered the eosinophil levels data and concluded that eosinophil levels should not be included in the indication statement for mepolizumab as a benefit in reduction of exacerbations could be observed for all levels of blood eosinophils in a combined analysis of DREAM and MENSA (Section 4.9). Expectedly, an increased efficacy of mepolizumab can be observed with an increase in blood eosinophil levels at baseline. However, to ensure an efficient use of NHS resources, GSK sought to identify a population for targeted add-on mepolizumab

therapy that are easily identifiable in clinical practice and have a greater capacity to benefit.

The threshold of eosinophil blood count that predicts a ≥30% reduction in the rate of exacerbation (established as clinically meaningful based on clinical precedent) is identified (i.e. eosinophil blood count in cells/µl that predicts a ≥30% decrease in rate of exacerbation)using a modelling concept as shown in Figure 7. A post-hoc analysis of the DREAM data identified patients with an increased response to mepolizumab (≥30% reduction in rate of exacerbations) with a blood eosinophil count of ≥150 cells/µL at initiation of treatment. This blood eosinophil criterion, in addition to the baseline eosinophil count inclusion criterion in DREAM (300 cells/µL at any point in the last 12 months) as well as the identified patient baseline criteria from the Proof-of-Concept studies (high dose ICS + additional maintenance treatment[s] and ≥2 exacerbations in the last 12 months), were then taken forward into the phase III patient inclusion criteria (MENSA and SIRIUS). Thus, MENSA and SIRIUS studied add-on mepolizumab therapy in a patient population identified in DREAM to have the most clinically meaningful benefit from this therapy (post hoc analysis of DREAM when applying the MENSA eosinophil inclusion criteria: Table 42, Section 4.8). Indeed, a post-hoc analysis of MENSA showed an even greater reduction in rate of exacerbation (39%) at the identified blood eosinophil threshold of ≥150 cells/µL (Figure 7). This observation formed the basis of the GSK proposed population to be treated with mepolizumab add-on therapy.

Figure 7 Modelling Analysis: Predicted Rate of Exacerbations by Baseline Blood Eosinophil Count (ITT results of DREAM and MENSA)



4.7.3.2 GSK proposed population

Mindful of NHS resources and ensuring biologics are targeted at those patients who would receive the greatest benefit we have explored and identified the GSK proposed population using three data driven criteria; eosinophil blood count ≥150, exacerbation rate ≥4 and systemic steroid use. Evidence for this approach and rationale is discussed below.

Eosinophil blood count

Pre-planned subgroup analysis of MENSA allowed the identification of a patient subpopulation that received additional clinical benefit from therapy with mepolizumab. An analysis of rate of clinically significant exacerbations by blood eosinophil inclusion criteria in the MENSA ITT population treated with mepolizumab 100mg SC (and 75mg IV), showed that subjects with ≥150 cells/μL baseline blood eosinophils at screening showed a higher reduction in exacerbation vs. placebo than subjects with ≥300 cells/μL baseline blood eosinophils documented in the previous 12 months (100mg SC: 74%, CI 0.14, 0.52 vs. 18%, CI 0.38, 1.73 [Table 20]). This was further supported by additional analysis of DREAM data (Table 43, Section 4.8) and MENSA data (Table 44 and Section 4.8). This trend was also confirmed in a post-hoc meta-analysis of DREAM and MENSA Table 21.

Table 20 Analysis of Rate of Clinically Significant Exacerbations by Blood Eosinophil Inclusion Criteria (MENSA, ITT Population)

Blood eosinophil inclusion criteria group	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
≥300/μL in the previous 12 months OR ≥150/μL at screening[2]			
≥300/μL documented in the previous 12 months			
n	23	34	39
Exacerbation rate/year	1.53	1.61	1.24
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo)		1.06	0.82
95% CI		0.49, 2.30	0.38, 1.73
≥150/μl demonstrated at screening			
n	69	59	48
Exacerbation rate/year	1.92	0.54	0.49
Comparison vs. Placebo			
Rate ratio (mepolizumab/placebo)		0.28	0.26
95% CI		0.15, 0.52	0.14, 0.52
Both (≥300/μL in the previous 12 months AND ≥150/ μL at screening)			
n	98	96	107
Exacerbation rate/year	1.62	0.98	0.74
Comparison vs. Placebo			
Rate ratio (mepolizumab/placebo)		0.60	0.46
95% CI		0.41, 0.88	0.31, 0.67

1. Thirteen subjects are not shown in this analysis due to having no eosinophil count measured at screening.
2. Three subjects did not meet either of the two blood eosinophil inclusion criteria and so are not present in this table.
Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented

with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable) and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. Note: For this analysis, Canada is combined with Rest of World within the covariate of region.

Table 21 Meta-Analysis of Rate of Clinically Significant Exacerbations by Blood Eosinophil Inclusion Criteria (DREAM and MENSA, all doses, ITT Population)

	Blood Eosinophils (cells/μL)	n	Rate Ratio Mepolizumab/Placebo (95% CI)	% Reduction in Exacerbations
Baseline only	≥150 cells/μL at treatment start No evidence of ≥300 cells/μL in previous 12 months	215	0.44 (0.29, 0.67)	56%
Historical only	≤150 cells/μL at treatment start Evidence of ≥300 cells/μL in previous 12 months	149	0.67 (0.42, 1.08)	33%

Exacerbation rate

Exploratory multivariate modelling was performed to investigate baseline variables predictive of overall number of exacerbations and of differential efficacy of mepolizumab. MENSA mepolizumab treatment groups were combined in this analysis.

This modelling showed that the covariates influencing the overall number of exacerbations were: treatment; blood eosinophil counts at screening; exacerbations in the year prior to screening; and baseline maintenance oral glucocorticosteroid use.

In DREAM a planned subgroup analysis of exacerbation reduction based on history of exacerbations in the last 12 months showed an increased reduction in exacerbation rate in subjects who had experienced more exacerbations (Figure 14, Section 4.8). The interaction between the number of previous exacerbations and treatment group was significant (p=0.014). However, regardless of exacerbation history, in MENSA subjects receiving mepolizumab 75 mg IV and 100 mg SC achieved a greater reduction in the frequency of exacerbations than those treated with placebo: subjects with 2 previous exacerbations reported 43% and 47% reduction respectively; subjects with 3 previous exacerbations reported 44% and 70% reduction respectively; and subjects with 4 or more previous exacerbations reported 60% and 56% reduction respectively (Table 22).

In MENSA, when looking at the predictive rate reduction of exacerbations from baseline based on the history of exacerbations in the previous 12 months and blood eosinophil count at screening, subjects with a higher historic exacerbation rate showed a clinically higher numerical reduction of exacerbations per annum (Figure 8). The same was observed in the earlier dose ranging study DREAM (Figure 11, Section 4.8).

Figure 8: Predictive modelling of rate of exacerbations based on blood eosinophil count at screening, history of exacerbations and treatment with mepolizumab or placebo (MENSA, ITT Population)

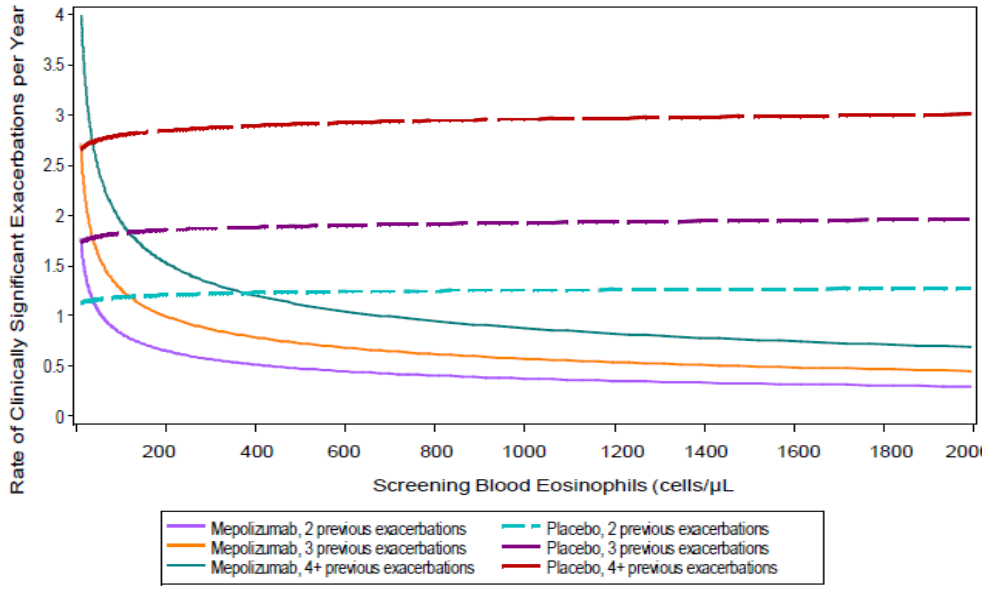


Figure adapted from Ortega et al. 2014

Table 22 Analysis of Rate of Clinically Significant Exacerbations by Previous Exacerbations (MENSA, ITT Population)

Previous exacerbation group	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
Previous exacerbations: 2			
n Exacerbation rate/year	90 1.09	82 0.61	74 0.58
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo) 95% CI		0.57 0.33, 0.96	0.53 0.30, 0.94
Previous exacerbations: 3			
n Exacerbation rate/year	46 1.63	47 0.91	48 0.48
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo) 95% CI		0.56 0.33, 0.94	0.30 0.16, 0.55
Previous exacerbations: ≥4			
n Exacerbation rate/year	55 3.22	62 1.29	72 1.43
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo) 95% CI		0.40 0.25, 0.64	0.44 0.29, 0.69

Note: Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable) and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. Note: For this analysis, Canada is combined with Rest of World within the covariate of region.

In summary, from these sub-analyses, patients with ≥150 cells/µl baseline blood eosinophils at screening and ≥4 exacerbations in the 12 months prior to screening, experienced the most benefit from therapy with add-on mepolizumab. The clinical viability of this conclusion was supported by independent severe asthma specialists'

interpretation of the results. Of note, this is consistent with NICE guidance for omalizumab that recommends ≥4 exacerbations (OCS bursts) as a criterion for use (described as frequent courses of OCS). Whilst we acknowledge the EMA concluded that eosinophil levels were not sufficiently predictive to justify a specific cut off level in the indication statement we believe the correlation is sufficient to justify use in identifying a target population with enhanced benefit to be considered for NICE guidance when both cost and clinical effectiveness are criteria for decision making.

Systemic corticosteroid use

Clinical opinion is that patients on maintenance OCS experience an additional clinical benefit from a reduction in OCS use. In SIRIUS the odds of patients reducing their OCS dose was 2.39 vs. SOC (ITT, 95% CI 1.25 – 4.56, p=0.008, Section 4.7.5.6). The main benefit of a reduction in OCS is the decreased burden of short- and long-term side effects of systemic corticosteroids. However, this benefit is difficult to capture in clinical trials and indeed patients receiving OCS show benefit in terms of asthma control, including a reduction in exacerbations. Thus, while add-on therapy with mepolizumab reduces the need for OCS, the relative benefit in terms of asthma control is reduced by the impact of the OCS treatment. This trend could be observed in the ITT population results in MENSA; mepolizumab reduced exacerbation rate of non-OCS users by 47% to 66% versus 20% to 48% in OCS users (Table 46, Section 4.8.1.5). Nonetheless, in patients on maintenance OCS with less than 4 exacerbations in the previous year, clinician's feedback was that a reduction in systemic corticosteroid exposure while maintaining asthma control was an additional major therapy objective of add-on mepolizumab therapy. We therefore also propose to include those patients dependent on maintenance OCS in our target population irrespective of exacerbation history. Given that the benefit on asthma control in those on maintenance OCS may be reduced we will present the results for our proposed population both including and excluding the patients on maintenance OCS with less than 4 exacerbations.

Summary of GSK proposed population

In summary we propose the following target population to provide an enhanced clinical benefit for patients and have presented the evidence demonstrating clinical and cost effective use of NHS resources in this proposed population.

Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/µl at initiation of treatment; and ≥4 exacerbations in the previous year or dependency on systemic corticosteroids (maintenance OCS).

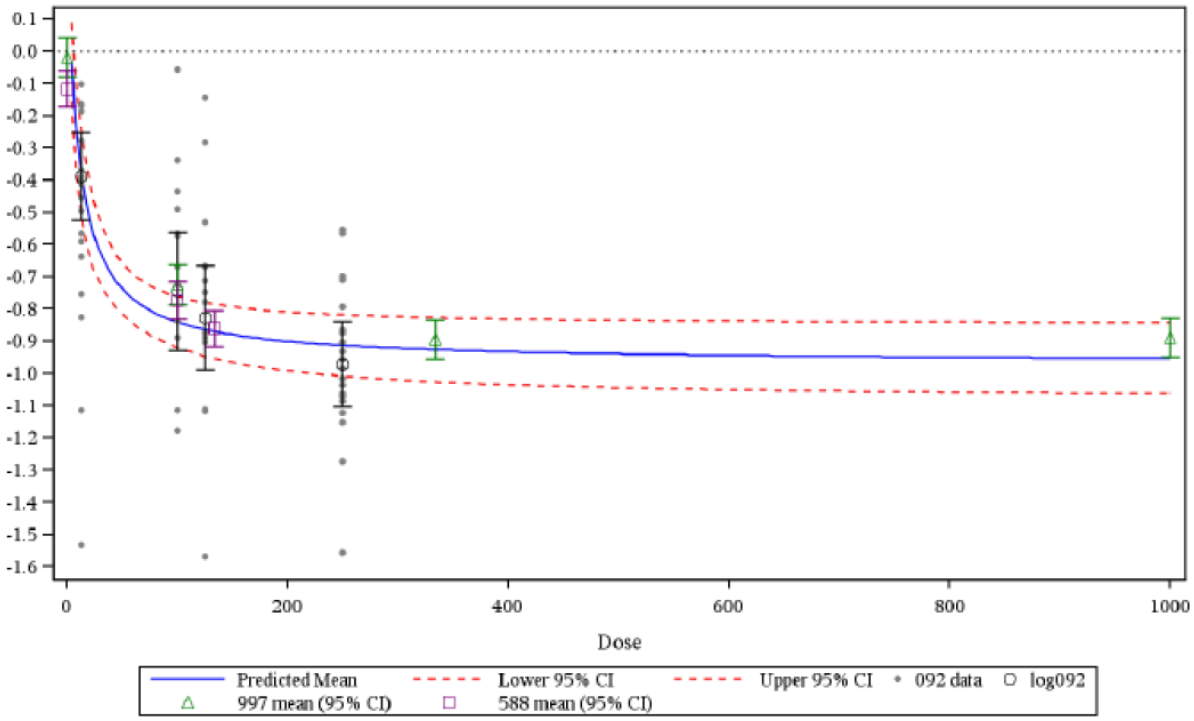
We have demonstrated that this GSK proposed population responds to mepolizumab with enhanced clinical benefits in terms of a reduction in clinically significant exacerbations, an improvement in asthma control and a reduction of mOCS use, thus reducing the risk of OCS's significant side effects, while maintaining asthma control. This patient population exists in the UK and is readily identifiable in current clinical practice as part of current severe asthma assessment standards. In addition, the blood eosinophil count, for identification of patients likely to respond to

mepolizumab, is taken as part of routine patient assessment. By selecting patients with ≥4 exacerbations in the past year or dependency on mOCS, it is also consistent with the current NICE guidance for omalizumab.

Rational for results presented

The EMA licensed posology for add-on mepolizumab therapy is 100mg subcutaneous (SC) injection. The PK/PD study (MEA114092), which was carried out in adult asthmatic subjects with elevated blood eosinophil levels demonstrated a clear dose response for blood eosinophil reduction via the SC route at doses from 12.5 to 250 mg every 4 weeks and at an IV dose of 75 mg.[117] A model-based analysis showed that the ID_{90} was approximately 100 mg SC, which corresponds to 75 mg IV (mepolizumab SC absolute bioavailability was approximately 75%). This model was validated by superimposing the IV data from DREAM (Figure 9).

Figure 9 Dose Response Ratio Compared to Baseline in Blood Eosinophils (Geometric Mean +/- Standard Error) In Adult Asthmatic Subjects with Elevated Blood Eosinophils (Data from DREAM and MENSA superimposed)



Note: IV dose displayed=SC dose equivalent (i.e., IV dose/0.75 based on assumed bioavailability; estimate from study SB-240653/018 Note: 'log092'=Baseline-adjusted least square mean estimate (95% CI) from PK/PD study
Note: "997" represents the DREAM study; "588" represents the MENSA study

Bioequivalence was further confirmed with MENSA data following 75mg IV and 100mg SC administration. In line with the marketing authorisation and in view of the proven bioequivalence between 100mg SC and 75mg IV this section will discuss the results for the SC and IV arms for the GSK proposed population. For the same reason, in the cost effectiveness model (section 5) 100mg SC and 75mg IV results were combined to ensure greater sensitivity. As MENSA and SIRIUS studied the appropriate patient population, identified as responders in the earlier development program, the discussion of the clinical section will focus on the GSK proposed subgroup from phase III trials, MENSA and SIRIUS:

1. GSK proposed population

MENSA

- Subjects with ≥150 cells/µl baseline blood eosinophils at initiation of treatment; and ≥4 exacerbations in previous year or dependency on maintenance OCS use with < 4 exacerbation in the previous year

SIRIUS (a patient population on maintenance OCS [mOCS]):

- ≥150 cells/µl baseline blood eosinophils at initiation of treatment

2. GSK proposed population excluding mOCS users with <4 exacerbations in the previous year

MENSA

- Subjects with ≥150 cells/µl baseline blood eosinophils at initiation of treatment, and ≥4 exacerbations in previous year

In SIRIUS, no exacerbation inclusion criterion was required as all patients fulfil the criterion of being dependent on maintenance OCS use. Thus, by selecting the SIRIUS population with ≥150 cells/µL baseline blood eosinophils at initiation of treatment represents the GSK proposed population. A subgroup analysis of ≥4 exacerbations in the past year was not feasible in this trial as the number of subjects would have been reduced significantly in the individual treatment arms (to <30 subjects per arm).

4.7.4 GSK proposed population results (MENSA & SIRIUS)

Specific analyses of the proposed population are only available for the most relevant end points to the decision problem and the cost effectiveness analysis. These are presented in full below. Some endpoints were deemed not relevant to the decision problem and, due to the reduced number of patients, not all the analyses are sufficiently powered to demonstrate statistical significance. Therefore, the less relevant endpoints are presented in the context of the results of the ITT population where appropriate or can be found in the CSRs.

4.7.4.1 Exacerbation rate (MENSA)

Table 23 Analysis of Rate of Clinically Significant Exacerbations (GSK proposed population)

MENSA	GSK proposed population excluding mOCS users with <4 exacerbations			GSK proposed population		
Rate of Clinically Significant Exacerbations	Placebo N=48	Mepolizumab 100mg SC N=54	Mepolizumab 75mg IV N=48	Placebo N=64	Mepolizumab 100mg SC N=78	Mepolizumab 75mg IV N=65
n	45	54	48	64	78	65

Exacerbation rate/year	**3.10**	**1.22**	**1.20**	**2.65**	**1.32**	**1.06**
Comparison vs. Placebo						
Rate ratio (mepolizumab/ placebo)	---	**0.39**	**0.39**	---	**0.50**	**0.40**
(95% CI)	---	**(0.23,0.67)**	**(0.22,0.68)**	---	**(0.32,0.78)**	**(0.24,0.67)**
p-value	---	**<0.001**	**<0.001**	---	**0.002**	**<0.001**

Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. Note: Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, region, and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable.

A 61% reduction in the rate of clinically significant exacerbations over placebo in the GSK proposed population excluding mOCS users with <4 exacerbations was observed, both in the SC and IV arm. When patients on OCS with less than 4 exacerbations (GSK proposed population) were included in the post-hoc analysis, as expected the reduction in clinically significant exacerbations, while still clinically significant, was slightly reduced (100mg SC: 50%, 75mg IV 60%). As mentioned above, this effect can be explained by the masking effect of mOCS therapy, while not accounting for the OCS sparing effects. Arguably, therefore the patient population excluding mOCS users gives a more true reflection of the benefit of add-on mepolizumab therapy. Compared to the ITT population the GSK proposed population excluding mOCS users has an increased reduction in clinically significant exacerbations (SC: 61% vs. 53%, respectively, Section 4.7.5.1). Reductions in rate of exacerbations can have significant impact on patients' quality of life (see section 4.7.4.3). In addition this can impact on work productivity and activity as well as healthcare utilisation. Indeed, this was observed in the patients on add-on mepolizumab therapy compared to placebo in the ITT population (appendix 8.5).

4.7.4.2 Emergency Department Visits and/or Hospitalisation (MENSA)

Table 24 Analysis of Rate of - Exacerbations Requiring Emergency Department Visits and/or Hospitalisation (GSK proposed population excluding mOCS users with <4 exacerbations)

MENSA	Placebo N=45	Mepolizumab 100mg SC N=54	Mepolizumab 75mg IV N=48
Rate of Exacerbations Requiring Hospitalisation or Emergency Department Visits[1]			
n	45	54	48
Exacerbation rate/year	**0.59**	**0.26**	**0.12**
Comparison vs. Placebo			
Rate ratio (mepolizumab/placebo)	---	**0.45**	**0.21**
(95% CI)	---	**(0.14,1.44)**	**(0.05,0.88)**
p-value	---	**0.177**	**0.033**
Rate of Exacerbations Requiring Hospitalisation[2]			
n	45	54	48

Exacerbation rate/year	**0.35**	**0.17**	**0.07**
Comparison vs. Placebo			
Rate ratio (mepolizumab/placebo)	---	**0.49**	**0.19**
(95% CI)	---	**(0.11,2.11)**	**(0.03,1.31)**
p-value	---	**0.338**	**0.091**

1. Note: Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. Note: Canada combined with Rest of World within the covariate of region.
2. Note: Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, region, and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable.

Table 25 Analysis of Rate of - Exacerbations Requiring Emergency Department Visits and/or Hospitalisation (GSK proposed population)

MENSA	Placebo N=64	Mepolizumab 100mg SC N=78	Mepolizumab 75mg IV N=65
Rate of Exacerbations Requiring Hospitalisation or Emergency Department Visits[1]			
n	64	78	65
Exacerbation rate/year	**0.52**	**0.26**	**0.16**
Comparison vs. Placebo			
Rate ratio (mepolizumab/placebo)	---	**0.49**	**0.31**
(95% CI)	---	**(0.19,1.31)**	**(0.10,0.99)**
p-value	---	**0.157**	**0.048**
Rate of Exacerbations Requiring Hospitalisation[2]			
n	64	78	65
Exacerbation rate/year	**0.29**	**0.16**	**0.08**
Comparison vs. Placebo			
Rate ratio (mepolizumab/placebo)	---	**0.55**	**0.28**
(95% CI)	---	**(0.15,2.03)**	**(0.05,1.45)**
p-value	---	**0.372**	**0.129**

1. Note: Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable.
2. Note: Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable.

In line with the reduction in exacerbations seen above, the GSK proposed populations had a reduction in the rate of exacerbations requiring emergency department visits and hospitalisation over placebo (Table 24 &

Table **25**). The same trend was observed in the rate of exacerbations requiring hospitalisation (Table 24 &

Table **25**).

Any reduction in exacerbations is a major benefit to patients and health care services; exacerbations associated with hospitalisation are the severest form of

these events, and are associated with considerable morbidity and mortality as well as a long term risk of accelerated lung function decline[118-120]

Of note, while a statistically significant reduction in ED visits and/or hospitalisations could be observed in the ITT population, there were very few such events (Section 4.7.5.2). By performing a subgroup analysis this number was further reduced. This meant that statistical analysis is less appropriate in this small subgroup and no conclusions should be reached for any differences between the subgroup and ITT results. Important events such as hospitalisations and emergency room visits are rare and difficult to characterise in single studies. Thus, in a meta-analysis of four studies (ITT population of DREAM, MENSA, SIRIUS and Haldar 2009) in patients with severe refractory eosinophilic asthma on appropriate standard of care therapy, treatment with mepolizumab approximately halved the rate of exacerbations requiring emergency department visits and/or hospitalisation compared to SoC and underlined the findings above (Section 4.9.2). In consideration of this and the fact that a comparable benefit in the rate of exacerbations is observed in the GSK proposed population vs. the ITT population, it is not an unreasonable assumption that a similar trend in rate of hospitalisations and emergency room visits may be observed in an adequately powered analysis of the GSK proposed population.

4.7.4.3 Quality of life: SGRQ (MENSA)

Table 26 Analysis of Change from Baseline in St. George's Respiratory Questionnaire (SGRQ) Score (GSK proposed population)

MENSA	**GSK proposed population excluding mOCS users with <4 exacerbations[1]**			**GSK proposed population[2]**		
SGRQ	**Placebo N=45**	**Mepolizumab 100mg SC N=54**	**Mepolizumab 75mg IV N=48**	**Placebo N=64**	**Mepolizumab 100mg SC N=78**	**Mepolizumab 75mg IV N=65**
n[1]	40	53	42	59	75	58
LS Mean (SE)	**42.4 (2.64)**	**29.5 (2.32)**	**32.5 (2.59)**	**41.3 (2.08)**	**31.3 (1.86)**	**33.4 (2.12)**
LS Mean Change (SE)	**-8.2 (2.64)**	**-21.1 (2.32)**	**-18.1 (2.59)**	**-8.7 (2.08)**	**-18.7 (1.86)**	**-16.6 (2.12)**
Comparison vs. Placebo						
Difference	---	**-12.8**	**-9.9**	---	**-10.00**	**-7.90**
(95% CI)	---	**(-19.9,-5.8)**	**(-17.2,-2.5)**	---	**(-15.5,-4.5)**	**(-13.8,-2.0)**
p-value	---	**<0.001**	**0.009**	---	**<0.001**	**0.008**

[1]Note: Only subjects with a Baseline and Week 32 assessment are included in the analysis. Note: Analysis performed using analysis of covariance with covariates of baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), baseline % predicted FEV_1, and treatment. [2]Note: Only subjects with a Baseline and Week 32 assessment are included in the analysis. Note: Analysis performed using analysis of covariance with covariates of baseline, region, baseline % predicted FEV_1, and treatment.

The GSK proposed population had a statistically and clinically significant improvement in SGRQ Score vs. placebo (Table 26). The minimal clinical important difference (MCID) for SGRQ is 4 units. The GSK proposed population achieved a two to three fold improvement of the MCID, suggesting that the selected subgroup indeed experiences a greater benefit from add-on mepolizumab therapy compared to the ITT population (-6.4 and -7 units, p<0.001, Section 4.7.5.3). The quality of life improvements were supported by the overall evaluation of response to therapy as rated by clinicians and subjects in the ITT population. At the end of the respective treatment periods, whether self-rated or clinician-rated, more subjects treated with mepolizumab 100 mg SC or 75 mg IV showed greater observable improvement (rated in categories of moderately or significantly improved) compared with subjects treated with placebo (see appendix 8.6). While a subgroup analysis of this data for the GSK proposed population is not available, it is likely that this would show greater observed improvement as was the case with the quality of life results for the GSK proposed population vs. the ITT population.

4.7.4.4 Asthma control: ACQ (MENSA)

Table 27 Analysis of Change from Baseline in Asthma Control Questionnaire (ACQ) Score at week 32 (GSK proposed population)

MENSA	**GSK proposed population excluding mOCS users with <4 exacerbations[2]**			**GSK proposed population[3]**		
ACQ	**Placebo N=45**	**Mepolizumab 100mg SC N=54**	**Mepolizumab 75mg IV N=48**	**Placebo N=64**	**Mepolizumab 100mg SC N=78**	**Mepolizumab 75mg IV N=65**
n[1]	40	51	41	58	73	57
LS Mean (SE)	**2.06 (0.139)**	**1.10 (0.125)**	**1.34 (0.136)**	**1.97 (0.113)**	**1.43 (0.114)**	**1.43 (0.114)**
LS Mean Change (SE)	**-0.27 (0.139)**	**-1.23 (0.125)**	**-0.98 (0.136)**	**-0.38 (0.113)**	**-1.17 (0.102)**	**-0.92 (0.114)**
Comparison vs. Placebo						
Difference	---	**-0.96**	**-0.72**	---	**-0.79**	**-0.54**
(95% CI)	---	**(-1.33,-0.59)**	**(-1.10,-0.33)**	---	**(-1.09,-0.49)**	**(-0.86,-0.23)**
p-value	---	**<0.001**	**<0.001**	---	**<0.001**	**<0.001**

1 Number of subjects with analysable data at the given time point [2]Note: Analysis performed using mixed model repeated measures with covariates of baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), baseline % predicted FEV_1, treatment, and visit, plus interaction terms for visit by baseline and visit by treatment group. [3]Number of subjects with analysable data at the given time point Note: Analysis performed using mixed model repeated measures with covariates of baseline, region, baseline % predicted FEV_1, treatment, and visit, plus interaction terms for visit by baseline and visit by treatment group.

The GSK proposed population had a statistically and clinically significant improvement in ACQ vs. placebo (Table 27). These improvements exceed the MCID

for ACQ of 0.5 in contrast to the ITT population results (-0.42 to -0.44, p<0.001, Section 4.7.5.4). This provides further evidence that the selected subgroup had added benefit from add-on mepolizumab therapy.

4.7.4.5 FEV_1 (MENSA)

Table 28 Analysis of Change from Baseline in Clinic Pre-Bronchodilator FEV_1 (mL) at week 32 for study MENSA (GSK proposed population)

MENSA	GSK proposed population excluding mOCS users with <4 exacerbations			GSK proposed population		
Pre-Bronchodilator FEV_1 (mL)	Placebo N=45	Mepolizumab 100mg SC N=54	Mepolizumab 75mg IV N=48	Placebo N=64	Mepolizumab 100mg SC N=78	Mepolizumab 75mg IV N=65
n[1]	40	53	43	59	76	59
LS Mean (SE)	**1855 (75.4)**	**1962 (67.3)**	**2002 (72.9)**	**1844 (59.1)**	**1960 (52.8)**	**1975 (59.3)**
LS Mean Change (SE)	**114 (75.4)**	**221 (67.3)**	**261 (72.9)**	**118 (59.1)**	**234 (52.8)**	**249 (59.3)**
Comparison vs. Placebo						
Difference	---	**107**	**148**	---	**116**	**131**
(95% CI)	---	**(-95,309)**	**(-59,355)**	---	**(-41,272)**	**(-35,296)**
p-value	---	**0.295**	**0.160**	---	**0.147**	**0.120**

1 Number of subjects with analysable data at the given time point. Note: Analysis performed using mixed model repeated measures with covariates of baseline, region, treatment and visit, plus interaction terms for visit by baseline and visit by treatment group.

The GSK proposed population had clinically but not statistically significant improvements in pre-bronchodilator FEV_1 vs. placebo (100mg SC: 107 ml and 116 ml; 75mg IV: 148 ml and 131 ml [Table 28]). There was a slightly higher numerical improvement compared to the ITT population's FEV_1 improvement (100mg SC: 98ml, p=0.028, Section 4.7.5.5). This showed a trend of improvement in the more severe GSK proposed population, in line with the ITT population results. Arguably with a bigger number of subjects, this could have reached statistical significance.

4.7.4.6 OCS dose (SIRIUS)

Table 29 Analysis of OCS Reduction During Weeks 20-24 (GSK proposed population)

SIRIUS	Number (%) Subjects	
	Placebo	Mepolizumab 100mg SC
n	48	54
90% - 100%	6 (13)	10 (19)
75% - <90%	5 (10)	9 (17)
50% - <75%	7 (15)	7 (13)
>0% - <50%	4 (8)	6 (11)

No change or any increase or lack of asthma control or withdrawal from treatment	26 (54)	22 (41)
Odds Ratio to Placebo 95% CI p-value		**1.81** **(0.86, 3.79)** **0.115**

Note: Analysed using a proportional odds model (multinomial (ordered) logistic generalised linear model), with terms for treatment group, region, baseline maintenance oral corticosteroids stratum (OCS use <5 yrs vs. OCS use ≥5 yrs) and baseline OCS dose (optimised dose).

The primary objective for maintenance OCS users is a reduction in OCS dose while maintaining asthma control. Thus a post-hoc analysis of SIRIUS in subjects with ≥150 cells/µl baseline blood eosinophils with no requirement (but not excluding) patients with exacerbations in the past year was performed. The analysis demonstrated a reduction in OCS use while maintaining asthma control in the GSK proposed population as shown in Table 29 & Table 30. However, as with a previous analysis of this subgroup the number of patients was reduced, which meant that the analysis was not sufficiently powered and thus did not reach statistical significance.

Table 30 Analysis of Secondary Endpoints of Reduction in Daily OCS Dose from Baseline (SIRIUS, GSK proposed population)

SIRIUS	**Placebo N=48**	**Mepolizumab 100mg SC N=54**
n for all secondary measures	48	54
≥50% Reduction in Daily OCS Dose, n (%)		
50% to 100%	18 (38)	26 (48)
<50%, no decrease in OCS, lack of asthma control, or withdrawal from treatment	30 (63)	28 (52)
Odds ratio to placebo	-	1.60
95% CI	-	(0.70, 3.64)
p-value	-	0.266
Reduction in Daily OCS Dose to ≥5 mg, n (%)		
Reduction to ≥5 mg	19 (40)	27 (50)
Reduction to >5 mg, lack of asthma control, or withdrawal from treatment	29 (60)	27 (50)
Odds ratio to placebo	-	1.64
95% CI	-	(0.68, 3.93)
p-value	-	0.268
Total Reduction of OCS Dose, n (%)		
Total (100%) reduction (0 mg)	4 (8)	7 (13)
OCS taken, lack of asthma control, or withdrawal from treatment	44 (92)	47 (87)
Odds ratio to placebo	-	1.35
95% CI	-	(0.32, 5.78)
p-value	-	0.684
Median Percentage Reduction in Daily OCS Dose		

Median (%)	0.0	36.5
95% CI of the median	(0.0, 50.0)	(0.0, 66.7)
Median difference	-	-14.3
95% CI of the median difference	-	(-50.0, 0.0)
p-value	-	0.162

Note: Analysed using a binary logistic regression model with terms for treatment group, region, baseline maintenance oral corticosteroids stratum (OCS use <5 yrs vs. OCS use ≥5 yrs) and baseline OCS dose (optimised dose).

More subjects treated with mepolizumab achieved an improvement in secondary endpoints (
Table **41**), which was consistent in demonstrating the benefit of mepolizumab in enabling the reduction of OCS dose.

Around half of subjects treated with mepolizumab achieved

- at least a 50% reduction in OCS dose compared with 38% of subjects receiving placebo

- a reduction of OCS dose to 5.0 mg compared with 40% of subjects treated with placebo.

The odds of OCS dose reduction were less and not statistically significant compared to the ITT population (Section 4.7.5.6). This could be a reflection of the fact that the subgroup analysis reduced the number of subjects, resulting in inadequate powering for statistical analysis and that the GSK proposed population represents a more severe patient population. The fact that the GSK proposed subgroup identified a more severe asthma population is supported by the fact that the majority of patients who experienced a reduction in OCS use in the ITT population were indeed represented in the GSK proposed population (≥50% reduction: 26 of 37 [70% of ITT]; ≤5mg: 27 of 37 [73% of ITT]; 100% reduction: 7 of 10 [70% of ITT]). This confirms that the GSK proposed population identified subjects that most benefit from add-on mepolizumab therapy.

Of note, by study design, subjects starting on lower doses had greater opportunity to be weaned from OCS; however, those starting on higher doses were not weaned from OCS completely to protect the subject from potential adrenal crisis.

4.7.4.7 Asthma control with OCS reduction (SIRIUS)

Table 31 Asthma Control Endpoint at Week 24 (SIRIUS, GSK proposed population)

SIRIUS	**≥150 cells/µL Baseline Blood Eosinophils**	
	Placebo	**Mepolizumab 100mg SC**
	n=48	n=54
Rate of Clinically Significant Exacerbations [1]		
Rate/Year	2.1	1.62
Comparison Mepo vs. Placebo	n=48	n=54
Rate Ratio (Mepo / Placebo)	-	0.77
95% CI	-	(0.51,1.17)
p-value	-	0.222

Rate of Exacerbations Requiring Hospitalisation or Emergency Department Visits[1]		
Rate/Year	0.2	0.07
Comparison Mepo vs. Placebo	n=48	n=54
Hazard Ratio (Mepo / Placebo)	-	0.33
95% CI	-	(0.06,1.72)
p-value	-	0.189
Change From Baseline in St George's Respiratory Questionnaire (SGRQ) Score[1]		
LS Mean (SE)	43.8 (2.17)	38.2 (2.03)
LS Mean Change (SE)	-3.5 (2.17)	-9.1 (2.03)
Comparison Mepo vs. Placebo	n=45	n=51
Difference to placebo	-	-5.6
95% CI	-	(-11.6,0.4)
p-value	-	0.066
Change From Baseline in Asthma Control Questionnaire (ACQ) Score[3]		
LS Mean (SE)	2.08 (0.150)	1.43 (0.143)
LS Mean Change (SE) -	-0.04 (0.150)	-0.69 (0.143)
Comparison Mepo vs. Placebo	n=42	n=45
Difference to placebo	-	-0.65
95% CI	-	(-1.06,-0.24)
p-value	-	0.002
Change From Baseline in Clinic Pre-Bronchodilator FEV_1 (mL)[4]		
LS Mean (SE)	1896 (66.2)	2036 (62.3)
LS Mean Change (SE)	17 (66.2)	157 (62.3)
Comparison Mepo vs. Placebo	n=46	n=52
Difference to placebo	-	140
95% CI	-	(-41,321)
p-value	-	0.129

All investigator defined exacerbations were clinically significant exacerbations 1. Note: Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, baseline maintenance OCS stratum (OCS use <5 yrs vs. OCS use >=5 yrs), region and dose of OCS at baseline, and with logarithm of time on treatment as an offset variable. 2. Note: Only subjects with a Baseline and Week 24 assessment are included in the analysis. Note: Analysis performed using analysis of covariance with covariates of baseline, region, baseline maintenance OCS stratum (OCS use <5 yrs vs. OCS use >=5 yrs), dose of OCS at baseline and treatment. 3. Number of subjects with analysable data at the given time point Note: Analysis performed using mixed model repeated measures with covariates of baseline, region, baseline maintenance OCS stratum (OCS use <5 yrs vs. OCS use >=5 yrs), dose of OCS at baseline, treatment and week, plus interaction terms for week by baseline and week by treatment group. 4. Number of subjects with analysable data at the given time point Note: Analysis performed using mixed model repeated measures with covariates of baseline, region, baseline maintenance OCS stratum (OCS use <5 yrs vs. OCS use >=5 yrs), dose of OCS at baseline, treatment and visit, plus interaction terms for visit by baseline and visit by treatment group.

Importantly, despite a meaningful reduction in maintenance OCS use, asthma control was maintained (Table 31 & ITT results Section 4.7.5.7). However, as discussed above, by selecting a specific subgroup of patients for the GSK proposed population, resulting in a reduction in the number of patients, statistical significance was not achieved. A clinically significant improvement in SGRQ (-5.6, p=0.066) and clinically as well as statistically significant improvement in ACQ (-0.65, p =0.002) was observed (Table 31). Due to insufficient events no analysis of hospitalisation rate could be performed (ITT hospitalisations: 7 in placebo group vs. 0 in mepolizumab group).

4.7.5 ITT population results

Whilst presenting the clinical effectiveness results in the GSK proposed population it is important to review these results in the context of the clinical effectiveness in the total ITT population. In this population because of the greater patient numbers there is greater power to detect a statistical as well as clinically significant difference. Furthermore, not all endpoints in the clinical trials available are analysed in the proposed population.

DREAM, a phase IIb trial, aimed to evaluate the dose response based on efficacy and safety of three doses of mepolizumab (75mg, 250mg and 750mg IV) over a 52 week treatment period in subjects with severe uncontrolled refractory asthma. DREAM confirmed that mepolizumab produced clinically important reductions in clinically significant exacerbations that were not dose dependent (Table 32; see section 4.9 for DREAM results). This, in addition to the PK/PD study supported the dose that was taken into the phase III clinical trial program.

Table 32 Frequency of clinically significant exacerbations at week 52 in all doses (DREAM, ITT population)

	Intravenous Mepolizumab			Placebo
	75mg n=153	250mg n=152	750mg n=156	n=155
Exacerbation rate/year	1.24	1.46	1.15	2.40
Percent reduction	48%	39%	52%	
Rate ratio (95% CI)	0.52 (0.39, 0.69)	0.61 (0.46, 0.81)	0.48 (0.36, 0.64)	
p-value	<0.001	<0.001	<0.001	-

Both the EQ-5D and Asthma Quality of Life Questionnaire (AQLQ) were used in the phase IIb DREAM study. The EQ-5D is a generic marker for quality of life, developed to assess the effect of any medical intervention on quality of life in multiple disease areas. It is a self-administered questionnaire. It provides a less specific tool in the assessment of quality of life in specific diseases, such as asthma and may lack specificity and sensitivity to stratify subpopulations of a disease. The incorporation of health benefits in cost utility analysis using the EQ-5D published by the NICE Decision Support Unit in 2010 found that disease specific measure such as AQLQ and SGRQ showed greater degree of responsiveness than the generic EQ-5D[121]. Responsiveness of a quality of life measure becomes more important when looking at extreme subgroups of patients where a more sensitive tool is required to differentiate between them.

Indeed, in our clinical trial data, EQ-5D was not able to stratify the severe asthma population in DREAM, categorising a third of patients as in good health despite being severe refractory eosinophilic asthmatics. This clearly shows that EQ-5D is not a sensitive and specific enough tool to assess quality of life in severe asthmatics. As a result EQ-5D was not included in the phase III programme for mepolizumab.

Both AQLQ and SGRQ have been developed for the assessment of quality of life in asthma.

The AQLQ is a self-administered questionnaire developed to evaluate the impact of asthma treatments on the quality of life of asthma sufferers.[122] The AQLQ contains 32 items in four domains: symptoms, activity limitation, emotional function, and environmental stimuli. The response format consists of a 7-point scale ranging from 1 to 7 where 1 indicates total impairment and 7 indicates no impairment. The 32 items of the questionnaire are averaged to produce one overall quality of life score. Assuming a statistically significant result ($p<0.05$), the MCID in overall quality of life, or in quality of life for any of the individual domains, is a change of 0.5 points.[123]

The SGRQ is a well-established self-administered instrument designed to measure quality of life in patients with diseases of airway obstruction.[124] The SGRQ has been validated in patients with chronic airflow limitation, including both asthma and chronic obstructive pulmonary disease (COPD), and validity has been established across a range of respiratory diseases and severities.[124-126] The questionnaire consists of 50 items across three domains: impact on daily life, activity, and symptoms. The questionnaire is scored on a scale of 0-100 where higher scores indicate more limitations. The MCID of a 4-point reduction has been established for both asthma and COPD, again supporting the SGRQ as responsive to changes in disease activity in asthma.[125,127]

When comparing the AQLQ with the SGRQ, there are differences in the content of the questionnaires; these differences may impact the face validity (meaning that the questionnaire "looks" appropriate to the targeted population intended to sample) and responsiveness across different asthma phenotypes. Table 33 shows the contribution of each domain to the total score of each instrument, weighted by percent. Within each domain, there are also differences in the item content. The AQLQ primarily evaluates symptoms and symptom triggers while the SGRQ has more content evaluating attacks of breathlessness and other symptoms. The intensity of activity explored in the Activity domains of the two measures also differs. The AQLQ includes moderate and strenuous activity while the SGRQ includes a wide range of activity level providing less potential for floor and ceiling impacts. The SGRQ also includes items assessing functional limitations and impact on daily life associated with lung disease. The SGRQ has greater face validity with regard to aspects of asthma important to patients with severe asthma and frequent exacerbations (e.g., overall experience of impairment and functional limitations due to lung disease and less emphasis on symptom triggers and impacts of specific symptoms) compared with the AQLQ.

Table 33 Contribution of instrument domain by HRQL instrument

	AQLQ		**SGRQ**	
Domains	**Symptoms**	**37.5%**	**Impact on daily life**	**53.1%**
	Activity limitation	34.4%	Activity	30.3%
	Emotional function	15.6%	Symptoms	16.6%
	Environmental stimuli	12.5%		

Adapted from Juniper, 1992 and Jones, 1991

The AQLQ has been shown to be responsive in patients with severe allergic asthma[103,128] but not consistently responsive in other populations of patients with severe asthma.[43,129,130]

In contrast, the SGRQ has recently been shown by independent investigators to be effective in measuring health status of patients with severe asthma. In a cohort of severe asthma patients, the SGRQ discriminated between patients with frequent exacerbations (>2) compared to those with few (<2) exacerbations.[131] Additionally, in a study of patients with severe, uncontrolled asthma in Brazil,[132] the SGRQ total and domain scores were strongly correlated with both the ACQ and Asthma Control Test (ACT). Overall, evidence supports the SGRQ as having content validity, construct validity, and responsiveness in patients with severe asthma. Based on the utility of this tool in patients with severe asthma, the SGRQ was introduced as the quality of life instrument for the Phase III studies MENSA and SIRIUS.

In DREAM, mean change (SD) from baseline EQ-5D questionnaire index score at Week 52 was 0.07 (0.221); 0.08 (0.252); 0.11 (0.207); and 0.09 (0.195) in the placebo, mepolizumab 75 mg, 250 mg and 750 mg IV groups, respectively. Mean change (SD) from baseline EQ-5D VAS (visual analogue scale) score at Week 52 was 10.9 (20.96); 10.4 (19.16); 13.7 (18.27); and 13.7 (19.85) in the placebo, mepolizumab 75 mg, 250 mg and 750 mg groups, respectively. The mean change from baseline score on the VAS was greater in the mepolizumab groups than in the placebo group at most time points. Overall, these were small changes without significant implications.

The AQLQ[122] was a secondary efficacy endpoint in the exacerbation Study, DREAM. As discussed above, this quality of life instrument was not included in MENSA or SIRIUS as it was deemed not specific enough for the severe refractory asthma population. For the AQLQ, the minimal clinically meaningful change from baseline on the total score is 0.5 points.[123] This was achieved at most time points in all four groups, including placebo although the differences were not statistically significant.

Table 34 Analysis of Asthma Quality of Life Questionnaire Score at Week 52 (DREAM, ITT Population)

	Placebo N=155	Mepolizumab 75 mg IV N=153	Mepolizumab 250 mg IV N=152	Mepolizumab 750 mg IV N=156
n at Week 52 LS mean LS mean change (SE for mean and mean change)	123 4.92 0.71 (0.090)	128 5.00 0.80 (0.089)	127 4.97 0.77 (0.088)	129 5.14 0.93 (0.088)
Comparison vs. placebo[1]				
Difference (mepolizumab/placebo) (95% CI) p-value	--- --- ---	0.08 (-0.16, 0.32) 0.501	0.05 (-0.19, 0.29) 0.664	0.22 (-0.02, 0.46) 0.069

1. Analysis performed using mixed model repeated measures with covariates of baseline, region, baseline maintenance OCS therapy, exacerbations in the year prior to the study, baseline % predicted FEV_1, treatment, and visit, plus interaction terms for visit by baseline and visit by treatment group.

4.7.5.1 Exacerbation rate (MENSA)

Table 35 Analysis of Rate of Clinically Significant Exacerbations (MENSA, ITT Population)

MENSA	Placebo N=346	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=344
Rate of Clinically Significant Exacerbations			
n Exacerbation rate/year	191 1.75	194 0.81	191 0.93
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo) (95% CI) p-value	--- --- ---	0.47 (0.35, 0.63) <0.001	0.53 (0.39, 0.71) <0.001

[1]Analysis model as in footnote [1]; estimates based on weighting applied to each level of class variable determined from observed proportions.

4.7.5.2 Emergency Department Visits and/or Hospitalisation (MENSA)

Table 36 Analysis of Rate of Exacerbations Requiring Emergency Department visits and/or Hospitalisation (MENSA, ITT Population)

MENSA	Placebo N=191	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=191
Rate of Exacerbations Requiring Hospitalisation/ED Visits			
n Exacerbation rate/year	191 0.20	194 0.08	191 0.14
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo) 95% CI p-value	---- ---- ----	0.39 (0.18, 0.83) 0.015	0.68 (0.33, 0.41) 0.299
Rate of Exacerbations Requiring Hospitalisation			
n Exacerbation rate/year	191 0.10	194 0.03	191 0.06
Comparison vs. placebo[2]			
Rate ratio (mepolizumab/placebo) 95% CI p-value	---- ---- ----	0.31 (0.11, 0.91) 0.034	0.61 (0.23, 1.66) 0.334

[1]Analysis model as in footnote [1]; estimates based on weighting applied to each level of class variable determined from observed proportions

4.7.5.3 Quality of life: SGRQ (MENSA)

Table 37 Analysis of Change from Baseline in SGRQ Total Score at Week 32 (MENSA, ITT Population)

MENSA	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
SGRQ			
n at Week 32	177	174	184
LS mean	37.7	31.2	30.7
LS mean Change	-9.0	-15.4	-16.0
(SE for man and mean change)	(1.16)	(1.16)	(1.13)
Comparison vs. placebo[1]			
Difference (mepolizumab/placebo)	---	-6.4	-7.0
(95% CI)	---	(-9.7, -3.2)	(-10.2, -3.8)
p-value	---	<0.001	<0.001

1. Analysis performed using analysis of covariance with covariates of baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbations in the year prior to the study (as an ordinal variable), baseline % predicted FEV_1, and treatment.

A sensitivity analysis imputing any missing Week 32 total scores with the subject's baseline score demonstrated similar results, with a statistically significant greater decrease (improvement) in SGRQ total score compared with placebo at Week 32 for both mepolizumab groups (100 mg SC: difference of -6.7 points and 75 mg IV: difference of -5.9 points).

4.7.5.4 Asthma control: ACQ (MENSA)

Baseline ACQ scores were >1.5, indicating poor asthma control ('not well-controlled >1, confidence in inadequately controlled asthma ≥1.5[133]) even though subjects were receiving optimised standard of care. The MCID for ACQ in an asthma population is a reduction of ≥0.5.[133] Although mepolizumab resulted in a statistically significant improvement in ACQ this didn't reach the threshold of a clinically important difference compared to the GSK proposed population discussed above (Section 4.7.4.4).

Table 38 Analysis of Change from Baseline in ACQ Symptoms (ITT Population)

MENSA	Placebo N=191	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=191
ACQ			
n[1] at Week 32	184	189	179
n[2] at Week 32	170	173	161
LS Mean	1.70	1.26	1.28
LS Mean Change	-0.50	-0.94	-0.92
(SE for mean and mean change)	(0.069)	(0.068)	(0.070)
Comparison vs. placebo[1]			
Difference (mepolizumab/placebo)	----	-0.44	-0.42
(95% CI)	----	(-0.63, -0.25)	(-0.61, -0.23)
p-value	----	<0.001	<0.001

[1] Number of subjects with analysable data for one or more time points
[2] Number of subjects with analysable data at the given time point
Note: Analysis performed using mixed model repeated measures with covariates of baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), baseline % predicted FEV_1, exacerbations in the year prior to the study (as an ordinal variable), treatment, and visit, plus interaction terms for visit by baseline and visit by treatment group. Estimates for MENSA and DREAM+MENSA are based on weighting applied to each level of class variable determined from observed proportions. For the individual studies, region is as defined in the study. For the DREAM+MENSA meta-analysis, region is as defined for the meta-analysis and study is included as a covariate.

4.7.5.5 FEV_1

Table 39 Analysis of Change from Baseline in Pre-Bronchodilator FEV_1 (mL) (ITT Population)

MENSA	Placebo N=191	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=191
Pre-Bronchodilator FEV_1 (mL)			
n[1] at Week 32	189	192	188
n[2] at Week 32	179	185	176
LS Mean	1907	2005	2007
LS Mean change	86	183	186
(SE for mean and mean change)	(31.4)	(31.1)	(31.5)
Comparison vs. placebo[1]			
Difference (mepolizumab/placebo)	----	98	100
(95% CI)	----	(11, 184)	(13, 187)
p-value	----	0.028	0.025

[1] Number of subjects with analysable data for one or more time points
[2] Number of subjects with analysable data at the given time point
Note: Analysis performed using mixed model repeated measures with covariates of baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbations in the year prior to the study (as an ordinal variable), treatment, and visit, plus interaction terms for visit by baseline and visit by treatment group. Estimates for MENSA and DREAM+MENSA are based on weighting applied to each level of class variable determined from observed proportions. For the individual studies, region is as defined in the study. For the DREAM+MENSA meta-analysis, region is as defined for the meta-analysis and study is included as a covariate.

4.7.5.6 OCS dose (SIRIUS)

Mepolizumab demonstrated statistically significant and clinically relevant improvements compared with SoC for key endpoints of OCS reduction in SIRIUS. Subjects receiving mepolizumab 100 mg SC treatment achieved greater reductions in OCS dose (

Table **40**) during Weeks 20 to 24 while maintaining asthma control compared with placebo (p=0.008) (see endpoint of asthma control in sections 4.7.5.7). Secondary analyses were supportive of this primary endpoint.

Table 40 Analysis of OCS Percent Reduction from Baseline during Weeks 20-24 by Reduction Categories (SIRIUS, ITT Population)

Reduction from Baseline	Number (%) of Subjects	
	Placebo N=66	Mepolizumab 100 mg SC N=69
n	66	69
90% to 100%	7 (11)	16 (23)
75% to <90%	5 (8)	12 (17)
50% to <75%	10 (15)	9 (13)
>0% to <50%	7 (11)	7 (10)
No decrease in OCS, lack of astham control, or withdrawal from treatment	37 (56)	25 (36)
Odds ratio to placebo	----	2.39
95% CI	----	(1.25, 4.56)
p-value	----	0.008

Note: Analysed using a proportional odds model (multinomial [ordered] logistic generalized linear model), with terms for treatment group, region, duration of OCS use at baseline (<5 yrs vs. ≥5 yrs), and baseline OCS dose (optimised dose).

Table 41 Secondary Endpoints of Reduction in Daily OCS Dose from Baseline (SIRIUS, ITT Population)

Weeks 20-24	Placebo N=66	Mepolizumab 100 mg SC N=69
n for all secondary measures	66	69
≥50% Reduction in Daily OCS Dose[1], n (%)		
50% to 100% <50%, no decrease in OCS, lack of asthma control, or withdrawal from treatment	22 (33) 44 (67)	37 (54) 32 (46)
Odds ratio to placebo 95% CI p-value	---- ---- ----	2.26 (1.10, 4.65) 0.027
Reduction in Daily OCS Dose to ≤5 mg[1] n (%)		
Reduction to ≤5 mg Reduction to >5 mg, lack of asthma control, or Withdrawal from treatment	21 (32) 45 (68)	37 (54) 32 (46)
Odds ratio to placebo 95% CI p-value	---- ---- ----	2.45 (1.12, 5.37) 0.025
Total Reduction of OCS Dose[1], n (%)		
Total (100%) reduction (0 mg) OCS taken, lack of asthma control, or withdrawal From treatment	5 (8) 61 (92)	10 (14) 59 (86)
Odds ratio to placebo 95% CI p-value	---- ---- ----	1.67 (0.49, 5.75) 0.414
Median Percentage Reduction in Daily OCS Dose[2]		
Median (%) 95% CI of the median	0.0 (-20.0, 33.3)	50.0 (20.0, 75.0)
Median difference 95% CI of the median difference p-value	---- ---- ----	-30.0 (-66.7, 0.0) 0.007

1. Analysed using a binary logistic regression model with terms for treatment group, region, duration of OCS use at baseline (<5 yrs vs. □5 yrs), and baseline OCS dose (optimised dose).
2. The median difference and associated confidence intervals are derived using Hodges-Lehman estimation. P-values are from a Wilcoxon rank-sum test of mepolizumab vs. placebo. For subjects who withdrew from the study prior to the Maintenance Phase, a value equal to the minimum percent reduction in OCS use across all subjects was imputed for the analysis.

In SIRIUS by study design, subjects starting on lower doses had greater opportunity to be weaned from OCS; however, those starting on higher doses (25mg/day) were not weaned from OCS completely to protect the subject from potential adrenal crisis.

4.7.5.7 Asthma control with OCS reduction (SIRIUS)

Table 40 Asthma Control Endpoint at Week 24 (SIRIUS, ITT population)

SIRIUS	ITT population	
	Placebo	Mepolizumab 100mg SC

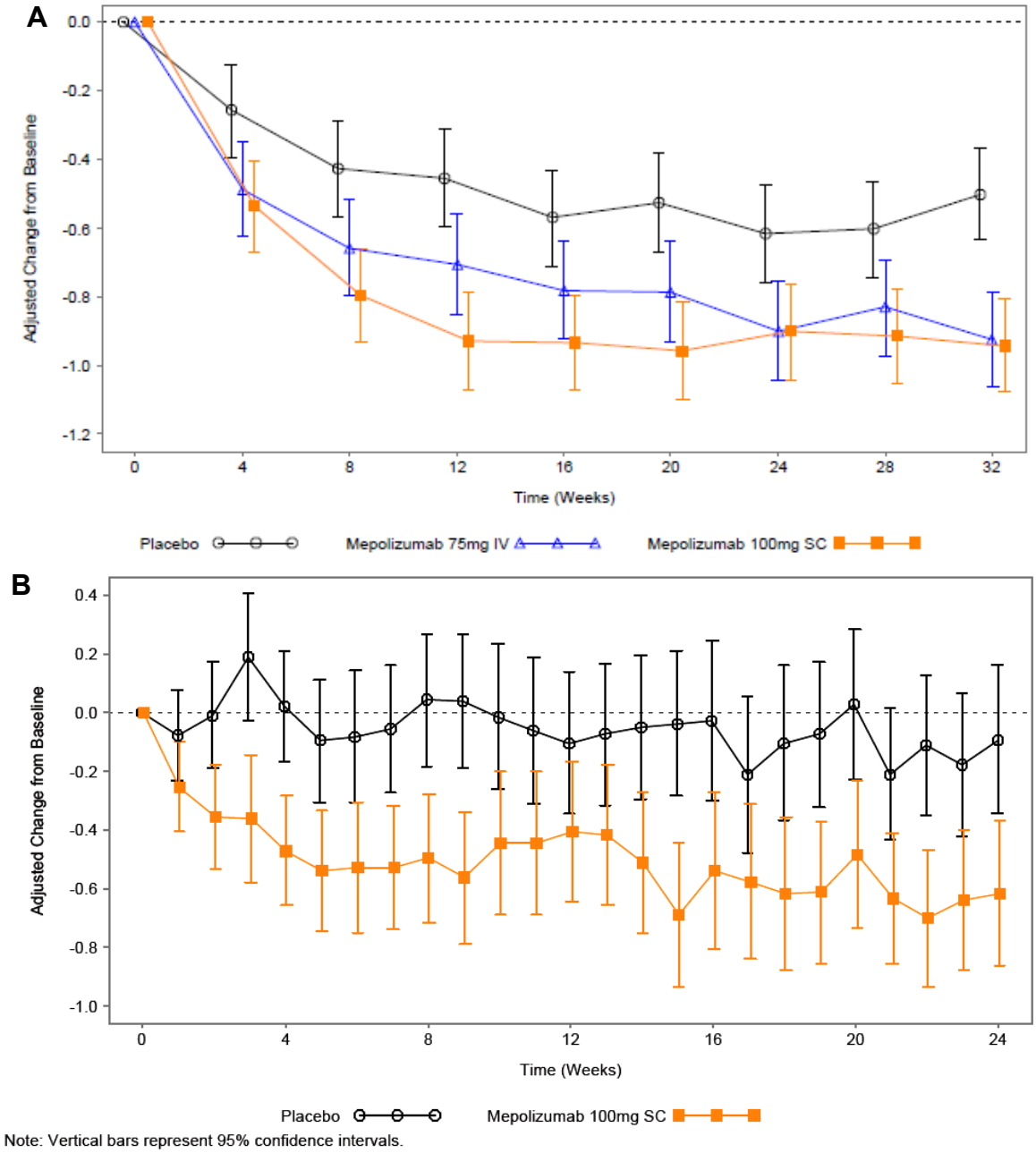
	n=66	n=69
Rate of Clinically Significant Exacerbations[1]	n=66	n=69
Rate/Year	2.12	1.44
Comparison Mepo vs. Placebo		
Rate Ratio (Mepo / Placebo)	-	0.68
95% CI	-	(0.47, 0.99)
p-value	-	0.042
Rate of Exacerbations Requiring Hospitalisation or Emergency Department Visits[2]	n=66	n=69
Rate/Year	10.7	4.5
Comparison Mepo vs. Placebo		
Hazard Ratio (Mepo / Placebo)	-	0.39
95% CI	-	(0.10, 1.50)
p-value	-	0.171
Change From Baseline in St George's Respiratory Questionnaire (SGRQ) Score[3]	n=61	n=65
LS Mean (SE)	44.3 (1.73)	38.5 (1.68)
LS Mean Change (SE)	-3.1 (1.73)	-8.8 (1.68)
Comparison Mepo vs. Placebo		
Odds ratio to placebo	-	-5.8
95% CI	-	(-10.6, -1.0)
p-value	-	0.019
Change From Baseline in Asthma Control Questionnaire (ACQ) Score[4]	n=53	n=58
LS Mean (SE)	1.98 (0.128)	1.46 (0.126)
LS Mean Change (SE) -	-0.09 (0.128)	-0.61 (0.126)
Comparison Mepo vs. Placebo		
Odds ratio to placebo	-	-0.52
95% CI	-	(-0.87, -0.17)
p-value	-	0.004
Change From Baseline in Clinic Pre-Bronchodilator FEV_1 (mL)[5]	n=62	n=66
LS Mean (SE)	1955 (56.5)	2070 (55.1)
LS Mean Change (SE)	-4 (56.5)	111 (55.1)
Comparison Mepo vs. Placebo		
Odds ratio to placebo	-	114
95% CI	-	(-42, 271)
p-value	-	0.151

All investigator defined exacerbations were clinically significant exacerbations 1. Insufficient events to perform analysis Note: Analysis performed using a Poisson model with covariates of treatment group, duration of OCS use at baseline (<5 yrs vs. ≥5 yrs), region, dose of OCS at baseline (optimised dose), and with logarithm of time on treatment as an offset variable. 2. Note: Estimated from Cox Proportional Hazards Model with covariates of treatment group, duration of OCS use at baseline (<5 yrs vs. ≥5 yrs), region, and dose of OCS at baseline (optimised dose). 3. Note: Analysis performed using analysis of covariance with covariates of baseline, region, duration of OCS use at baseline (<5 yrs vs. ≥5 yrs), dose of OCS at baseline (optimised dose), and treatment. 4. Note: Analysis performed using mixed model repeated measures with covariates of baseline, region, duration of OCS use at baseline (<5 yrs vs. ≥5 yrs), dose of OCS at baseline (optimised dose), treatment and week, plus interaction terms for week by baseline and week by treatment group. 5. Note: For pre-bronchodilator FEV_1, analysis performed using mixed model repeated measures with covariates of baseline, region, duration of OCS use at baseline (<5 yrs vs. ≥5 yrs), dose of OCS at baseline, treatment and week, plus interaction terms for week by baseline and week by treatment group. Note: Analysis performed using mixed model repeated measures with covariates of baseline, region, baseline maintenance OCS stratum (OCS use <5 yrs vs. OCS use >=5 yrs), dose of OCS at baseline,

4.7.5.8 Long-term efficacy

Long term efficacy of mepolizumab SC was demonstrated in MENSA (32 weeks) and SIRIUS (24 weeks). In these studies, there were sustained reductions in exacerbations, improvement in asthma control (Figure 10) and quality of life as well as a sustained reduction in corticosteroid dose while maintaining asthma control. Additional long term efficacy beyond these study periods were also obtained and will be discussed in the open label extension (OLE) studies section 4.11.

Figure 10 Repeated Measures Analysis of Change from Baseline in ACQ-5 Score (Study MENSA (A) and SIRIUS (B), ITT Population)



Note: Vertical bars represent 95% confidence intervals.

4.8 Subgroup analysis

Subgroup analyses were conducted based on pre-determined clinically relevant factors in order to investigate the consistency of the benefits observed with each interventional treatment. Explorative multivariate modelling was performed to investigate the baseline variable predictive of overall number of exacerbations and of differential efficacy of mepolizumab in DREAM and MENSA. In SIRIUS, further tabulations of the primary endpoint were performed to investigate the potential differential effects of mepolizumab. However, the results for the subgroup analyses in SIRIUS were somewhat limited and should be viewed with caution due to the small sample sizes of the treatment groups within the subgroups.

Subgroup analyses considered to be relevant to the decision problem have been discussed below and aim to provide additional information that is balanced in regards to the GSK proposed population presented in section 4.7; all other pre-planned subgroup analyses have been provided in the CSRs.

4.8.1.1 Subgroup analyses by demographic characteristics

Gender, age, race and geographic region subgroup analyses all showed that regardless of these characteristics, the subjects that were treated with mepolizumab achieved a greater reduction in the rate of clinically significant exacerbation than those treated with SoC alone.

When considering the DREAM and MENSA subgroup analysis by weight, there were no notable differences in the rate of clinically significant exacerbations. This was confirmed in a meta-analysis of weight-based dose response as listed in Section 4.9. For SIRIUS, the results also showed that subjects treated with mepolizumab achieved greater reductions in OCS dose compared to placebo, regardless of weight.

4.8.1.2 Baseline Blood Eosinophils

This section supports the discussion in section 4.7 and thus is presented in the order referenced in section 4.7. In addition, further data relevant to the decision problem are discussed. Subgroup analyses deemed not relevant to the decision problem can be found in the CSRs.

Table 42 Analysis of Rate of Clinically Significant Exacerbations for DREAM by Baseline Blood Eosinophil Criteria for MENSA (DREAM, ITT Population)

	Placebo N=155	Mepolizumab 75 mg IV N=153	Mepolizumab All Doses[2] N=461
MEA112997			
Met Eosinophil Criteria			
n	137	126	385
Exacerbation rate/year	2.42	1.18	1.18
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo)	---	0.49	0.49
(95% CI)	---	(0.35, 0.67)	(0.38, 0.63)
Did Not Meet Eosinophil Criteria			

n Exacerbation rate/year	18 2.07	27 1.52	76 1.82
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo) (95% CI)	--- ---	0.73 (0.35, 1.52	0.90 (0.49, 1.64)

1. Analysis performed using a negative binomial regression model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbation in the year prior to the study, and baseline % predicted FEV_1, with logarithm of time on treatment as an offset variable
2. Included 75, 250 and 750mg IV and 100mg SC.

Table 43 Analysis of Rate of Clinically Significant Exacerbations by Baseline Blood Eosinophil Levels >0.15 GI/L (150 cells/µL) vs. Blood Eosinophil Inclusion Criterion (DREAM)

	Placebo N=155	Mepolizumab (All Doses) N=461
Base Eos >0.15 GI/L and Blood Eos Inc Criteria Met		
n	79	225
Exacerbation rate/year	2.34	1.10
Comparison vs. placebo		
Rate ratio (mepolizumab/placebo)	-	0.47
95% CI	-	(0.33, 0.66)
Base Eos >0.15 GI/L and Blood Eos Inc Criteria Not Met		
n	38	113
Exacerbation rate/year	2.58	1.05
Comparison vs. placebo		
Rate ratio (mepolizumab/placebo)	-	0.41
95% CI	-	(0.26, 0.63)
Base Eos <0.15 GI/L and Blood Eos Inc Criteria met		
n	17	44
Exacerbation rate/year	1.77	1.31
Comparison vs. placebo		
Rate ratio (mepolizumab/placebo)	-	0.74
95% CI	-	(0.35, 1.59)
Base Eos <0.15 GI/L and Blood Eos Inc Criteria Not Met		
n	21	79
Exacerbation rate/year	1.47	1.51
Comparison vs. placebo		
Rate ratio (mepolizumab/placebo)	-	1.03
95% CI	-	(0.56, 1.90)

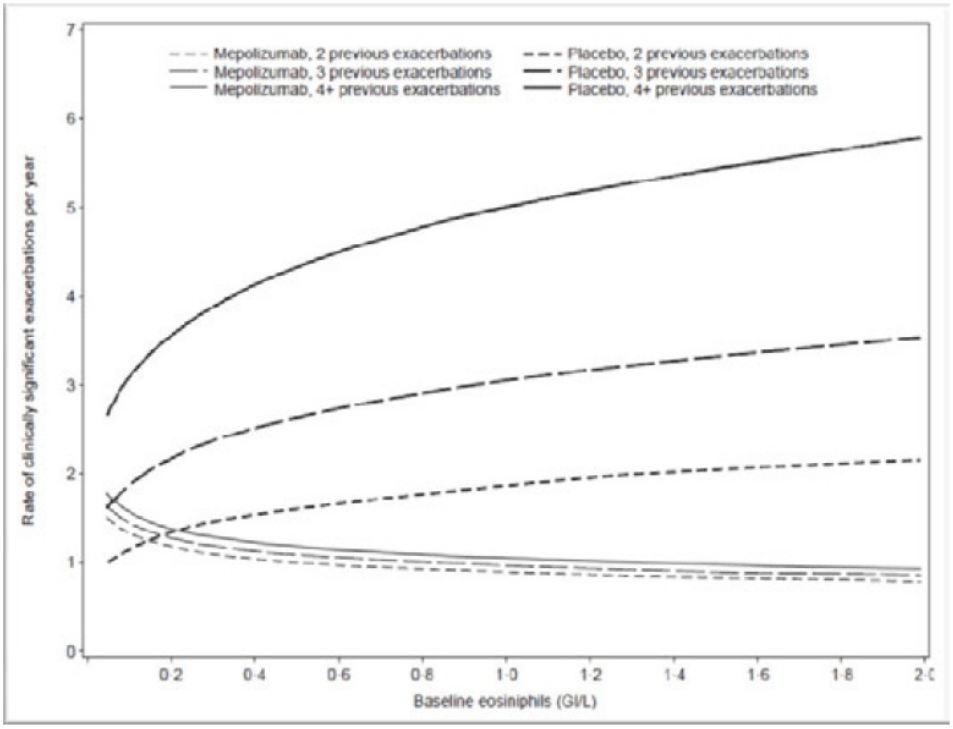
Baseline blood eosinophil inclusion criterion = peripheral blood eosinophil level □0.3 GI/L at Visit 1 or in the previous 12 months.

Table 44 Analysis of Rate of Clinically Significant Exacerbations by Blood Eosinophil Inclusion Criteria (MENSA, ITT Population)

Blood eosinophil inclusion criteria group	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
≥300/µL documented in the previous 12 months			
Inclusion: No			
n Exacerbation rate/year	70 1.89	61 0.51	48 0.50
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo) 95% CI		0.27 0.15, 0.51	0.27 0.14, 0.52
Inclusion: Yes			
n Exacerbation rate/year	121 1.64	130 1.13	146 0.94
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo) 95% CI		0.69 0.49, 0.98	0.57 0.41, 0.80
≥150/µL demonstrated at screening[1]			
Inclusion: No			
n Exacerbation rate/year	21 1.31	30 1.23	35 1.20
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo) 95% CI		0.94 0.43, 2.07	0.91 0.44, 1.90
Inclusion: Yes			
n Exacerbation rate/year	167 1.75	155 0.81	155 0.67
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo) 95% CI		0.46 0.33, 0.64	0.38 0.27, 0.53

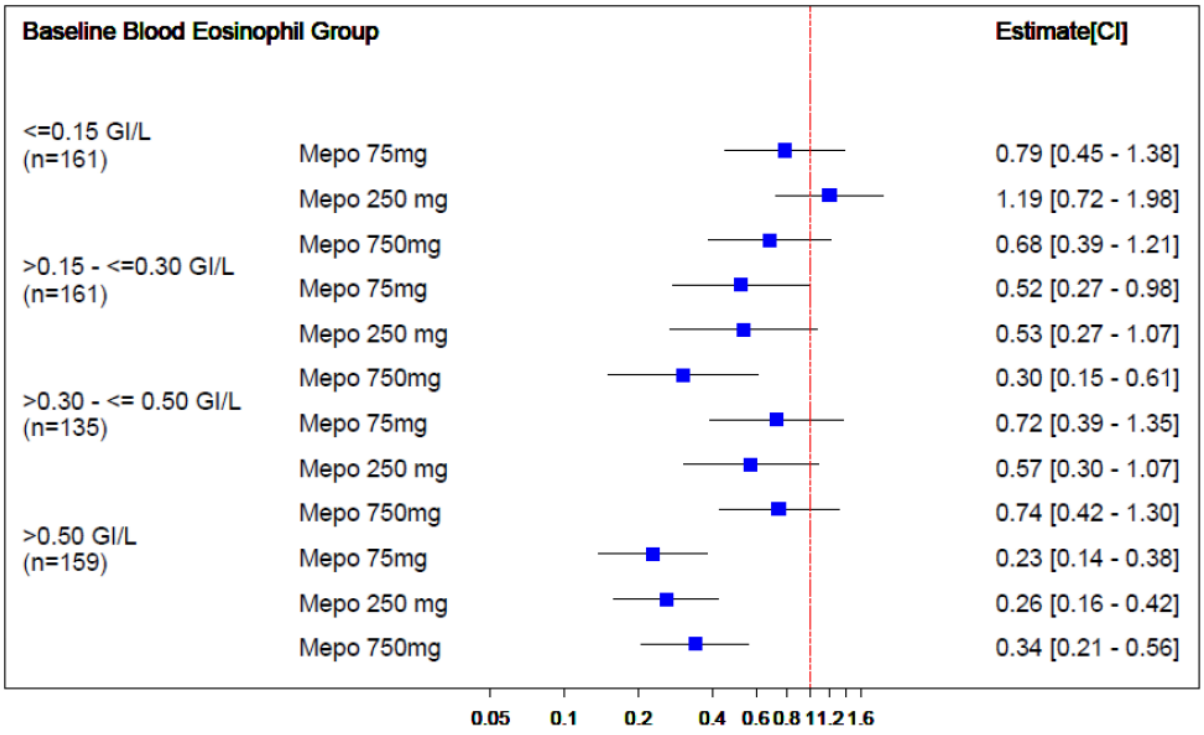
1. Thirteen subjects are not shown in this analysis due to having no eosinophil count measured at screening.

Figure 11 Predictive modelling of rate of exacerbations based on blood eosinophil count at baseline, history of exacerbations and treatment with mepolizumab or placebo (DREAM)



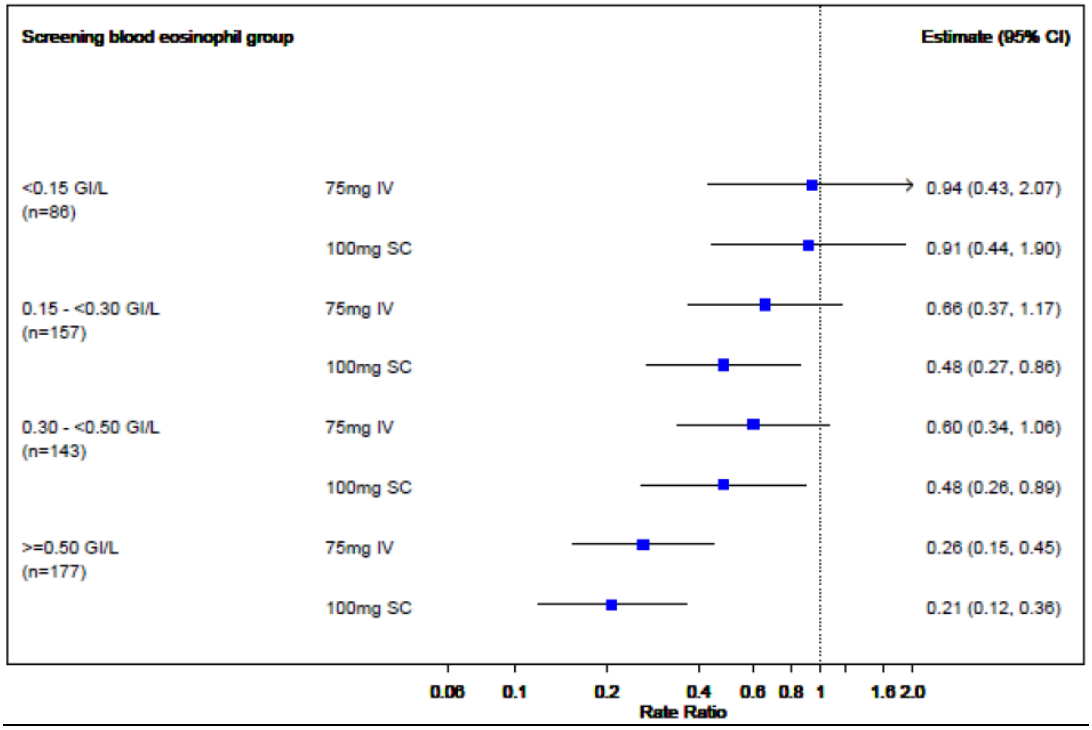
Subgroup analysis by baseline blood eosinophil group was carried out in DREAM, and is graphically represented below in Figure 12. In the subjects with ≤0.15 GI/L (150 cells/μL) blood eosinophils at baseline, there was a smaller decrease in rate of clinically significant exacerbations. There was a statistically significant interaction between baseline blood eosinophil group and treatment group.

Figure 12 Rate of Clinically Significant Exacerbations by Baseline Blood Eosinophils (DREAM, ITT Population, all IV doses)



When analysing the blood eosinophil level from the MENSA study, it could be seen that most of the subjects had both criteria of blood eosinophils at screening of 150 cells/μL or greater at initiation of treatment or the historical levels of 300 cells/μL in the prior year. Regardless of blood eosinophil levels at screening, subjects receiving mepolizumab 75mg IV and 100mg SC achieved a consistently greater reduction in the frequency of exacerbations than those treated with placebo (Figure 13). This was not the case for subjects with an eosinophil count of <150 cells/ μL at initiation of treatment. This subgroup analysis suggested a positive correlation between eosinophil count and percent reduction in clinically significant exacerbations.

Figure 13 Rate of Clinically Significant Exacerbations by Screening Blood Eosinophils (MENSA, ITT Population)



In SIRIUS, subgroup analysis was carried out by baseline eosinophil levels, all subgroups showed a positive effect of active treatment (Table 45). However, by splitting into subgroups the number of subjects in each group was significantly reduced it is difficult to draw a clear conclusion.

Table 45 Analysis of OCS Percent Reduction from Baseline during Weeks 20-24 by Baseline Eosinophil Level (SIRIUS, ITT Population)

Subgroup - Baseline Eosinophil Level	Number (%) of Subjects	
	Placebo N=66	Mepolizumab 100 mg SC N=69
<150 cells/µL		
n	18	15
90% to 100%	1 (6)	6 (40)
75% to <90%	0	3 (20)
50% to <75%	3 (17)	2 (13)
>0% to <50%	3 (17)	1 (7)
No decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment	11 (61)	3 (20)
Odds ratio to placebo	---	6.87
95% CI	---	(1.53, 30.88)
150 to <300 cells/µL		
n	20	18
90% to 100%	3 (15)	4 (22)
75% to <90%	2 (10)	2 (11)
50% to <75%	2 (10)	2 (11)
>0% to <50%	1 (5)	1 (6)

No decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment	12 (60)	9 (50)
Odds ratio to placebo 95% CI	--- ---	2.03 (0.53, 7.75)
300 to <500 cells/µL		
n 90% to 100% 75% to <90% 50% to <75% >0% to <50% No decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment	9 1 (11) 1 (11) 1 (11) 1 (11) 5 (56)	16 3 (19) 4 (25) 3 (19) 1 (6) 5 (31)
Odds ratio to placebo 95% CI	--- ---	3.64 (0.69, 19.24)
≥500 cells/µL		
n 90% to 100% 75% to <90% 50% to <75% >0% to <50% No decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment	19 2 (11) 2 (11) 4 (21) 2 (11) 9 (47)	20 3 (15) 3 (15) 2 (10) 4 (20) 8 (40)
Odds ratio to placebo 95% CI	--- ---	1.01 (0.31, 3.31)

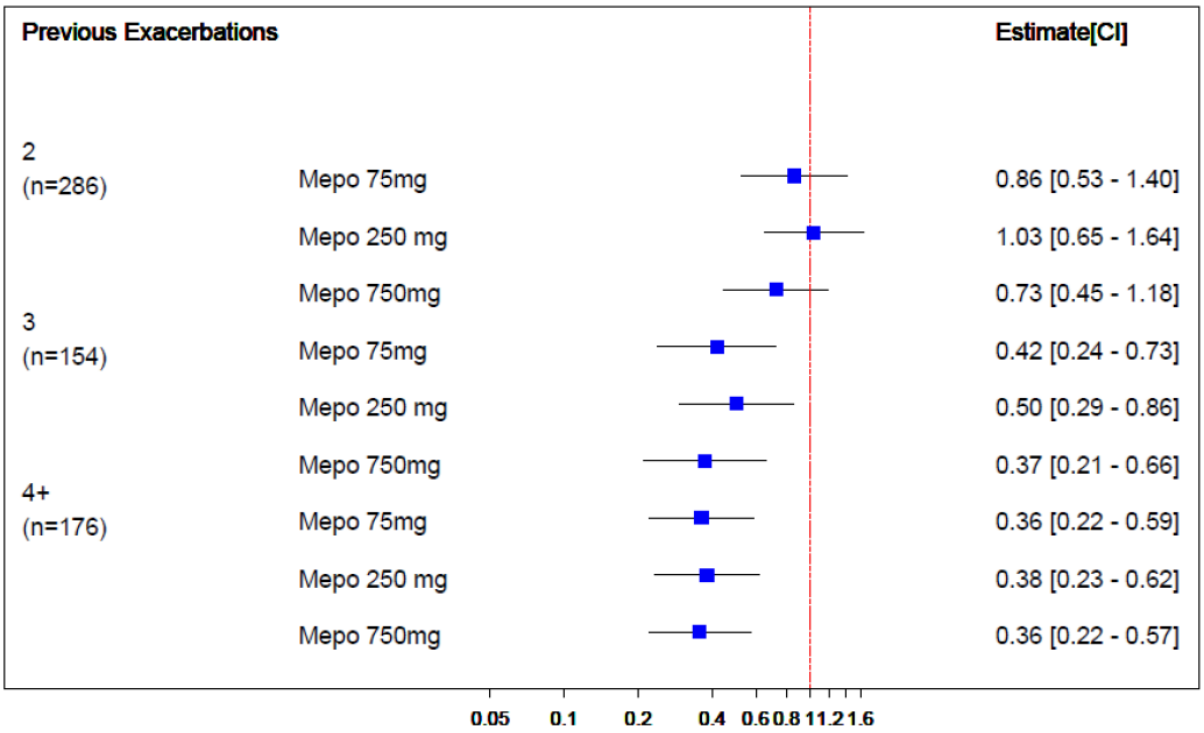
4.8.1.3 Baseline Percent Predicted Pre-Bronchodilator FEV_1

A subgroup analysis was carried out to analyse the rate of clinically significant exacerbations by baseline percentage predicted pre-bronchodilator FEV_1 in MENSA. Regardless of baseline percent predicted FEV_1, subjects receiving mepolizumab 75mg IV and 100mg SC achieving a greater reduction in the frequency of exacerbations than those treated with placebo: subjects with >60% percent predicted FEV_1 reported 42% and 43% reduction respectively; subjects with >60%-80% percent predicted FEV_1 reported 63% and 69% reduction respectively; and subjects >80% percent predicted FEV_1 reported 30% and 59% reduction respectively.

4.8.1.4 Previous exacerbations

Subgroup analyses were carried out in both DREAM and MENSA which looked at the previous exacerbations of the subjects, discussed in section 4.7. In the DREAM study, the interaction between the number of previous exacerbations and treatment group was potentially significant (p=0.014). There were larger decreases in exacerbations in the mepolizumab groups, compared with placebo, in subjects who had previously experienced more exacerbations (Figure 14).

Figure 14 Rate of Clinically Significant Exacerbations by Previous Exacerbations: Ratio to Placebo (DREAM)



NB: One subject in the placebo group and one subject in the mepolizumab 250mg group had fewer than two exacerbations in the 12 months prior to screening and were defined as protocol violators.

However, subjects with fewer exacerbations at baseline also tended to have lower baseline blood eosinophil counts at screening. The multivariate modelling of exacerbations by history of exacerbations and baseline blood eosinophil counts suggested that for those with a history of two exacerbations in the previous year, there appears to be a benefit in subjects with a baseline level of blood eosinophils above 150 cells/μL.

4.8.1.5 Baseline Maintenance Oral Corticosteroid Therapy

A subgroup analysis was carried out for MENSA, which looked at the analysis of rate of clinically significant exacerbations by baseline oral corticosteroid therapy.

In study MENSA, most of the subjects were not on maintenance OCS therapy (432/576 [75%]). Regardless of whether or not subjects received maintenance OCS therapy at baseline (Week 0), subjects receiving mepolizumab 75 mg IV and 100 mg SC achieved a greater reduction in the frequency of exacerbations than those treated with SoC alone (Table 46). Of note the reduction in exacerbations in subjects on OCS showed a clinically not significant reduction of 20% compared to 66% in the non-OCS users. A similar trend was observed in the GSK proposed population when compared to the GSK proposed population excluding maintenance OCS users, discussed in section 4.7.

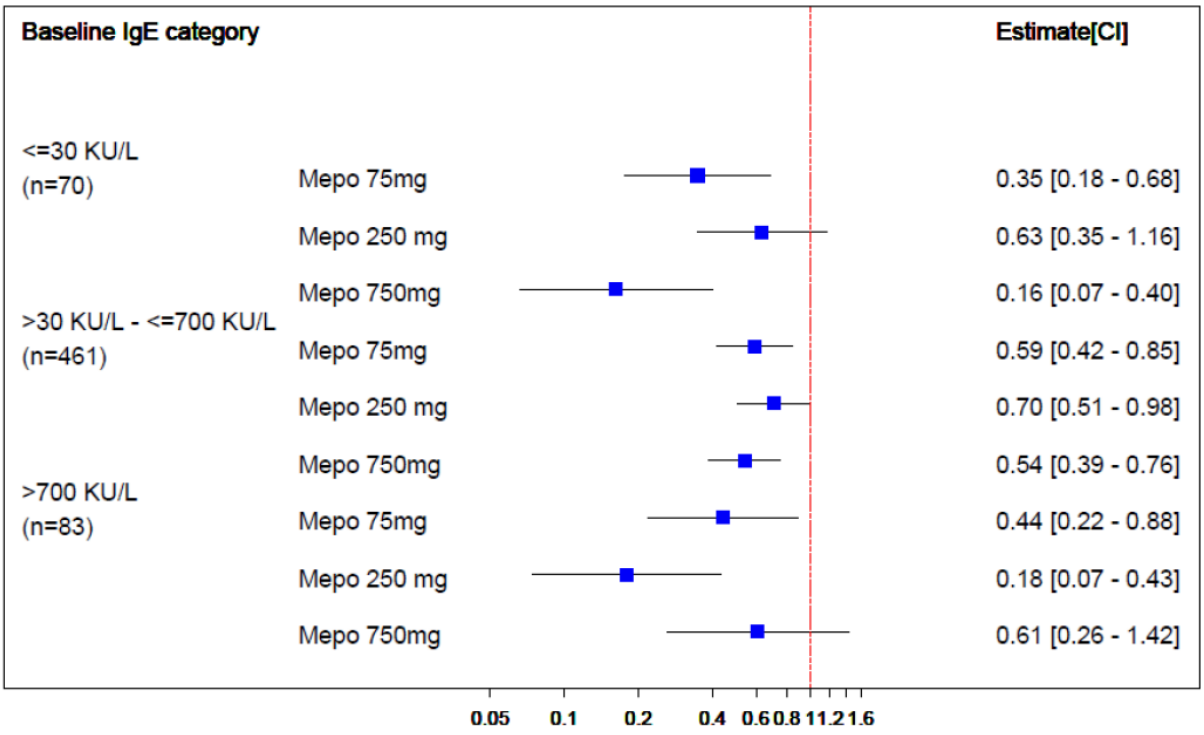
Table 46 Analysis of Rate of Clinically Significant Exacerbations by Baseline Maintenance Oral Corticosteroid Therapy (ITT Population, MENSA)

Baseline maintenance OCS therapy	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
No			
n Exacerbation rate/year	147 1.60	143 0.85	142 0.55
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo) 95% CI		0.53 0.37, 0.76	0.34 0.23, 0.51
Yes			
n Exacerbation rate/year	44 2.16	48 1.12	52 1.73
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo) 95% CI		0.52 0.31, 0.86	0.80 0.49, 1.29

4.8.1.6 Baseline IgE Concentration in DREAM and MENSA

A subgroup analysis was carried out in both DREAM and MENSA which looked at the rate of clinically significant exacerbations by baseline concentration of IgE. Data from the DREAM subgroup analysis is presented below in Figure 15.

Figure 15 Rate of Clinically Significant Exacerbations by Baseline Immunoglobulin E Concentration: Ratio to Placebo (DREAM)



There was an interaction between baseline total IgE concentration at baseline and treatment group (p=0.021). Multivariate modelling of response showed no differential effect of mepolizumab according to baseline total IgE concentration.

In study MENSA, most of the subjects had elevated levels of IgE > 100µ/mL. Irrespective of baseline IgE concentration, subjects receiving mepolizumab experienced a greater reduction in exacerbation frequency compared to placebo except for subjects in the mepolizumab 100mg SC group with ≤30 U/mL, although the population number was not very high for this subgroup (Table 47).

Table 47 Analysis of Rate of Clinically Significant Exacerbations by Baseline IgE Concentration (ITT Population, MENSA)

Baseline IgE concentration group	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
≤30 U/mL			
n Exacerbation rate/year	28 0.31	23 0.22	24 0.31
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo) 95% CI		0.73 0.34, 1.54	1.00 0.47, 2.10
>30 - ≤700 U/mL			
n Exacerbation rate/year	129 1.66	122 0.78	130 0.68
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo) 95% CI		0.47 0.33, 0.69	0.41 0.28, 0.60
>700 U/mL			
n Exacerbation rate/year	25 1.59	34 1.26	28 0.55
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo) 95% CI		0.79 0.37, 1.69	0.35 0.13, 0.90

Note: 34 subjects are not shown in this analysis due to not having IgE measured at baseline.

4.8.1.7 Prior Use of omalizumab in study MENSA

Most of the subjects did not have prior treatment experience with omalizumab. Treatment with omalizumab was not allowed during the MENSA study. The number of subjects that reported prior use of omalizumab was 21 (11%), 29 (15%) and 25 (13%), in the placebo, mepolizumab 75mg IV and mepolizumab 100mg SC treatments arms, respectively. There appeared to be no marked difference between the prior omalizumab and non-prior omalizumab users in the reduction of clinically significant exacerbations. However, due to the small numbers of prior omalizumab users, it is difficult to draw meaningful conclusions (Table 48).

Table 48 Analysis of Rate of Clinically Significant Exacerbations by Previous Omalizumab Use

Previous Omalizumab use	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
Yes			
n Exacerbation rate/year	21 2.36	29 0.65	25 1.40
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo) 95% CI		0.27 0.12, 0.65	0.59 0.28, 1.26
No			
n Exacerbation rate/year	170 1.62	162 0.99	169 0.74
Comparison vs. placebo			
Rate ratio (mepolizumab/placebo) 95% CI		0.61 0.45, 0.84	0.46 0.33, 0.63

4.9 Meta-analysis

4.9.1 Overview of Meta-analyses

A number of meta-analyses on the mepolizumab trial data have been completed (Table 49).

A meta-analysis looking at exacerbations requiring emergency department visit and/or hospitalisation was performed to get a better understanding of add-on mepolizumab therapy, as the incidence of such event was low in the individual clinical trials (Section 4.9.2).

A meta-analysis as part of the Integrated Summary of Efficacy (ISE) for the EMA and FDA regulatory submissions included two placebo-controlled exacerbation studies with similar design, DREAM and MENSA, to inform on a more precise effect size and to examine efficacy results across subgroups (Section 4.9.3).

The integrated treatment comparison of mepolizumab to omalizumab for patients with severe asthma with overlapping eosinophilic and allergic phenotypes is presented in section 4.10.

A further meta-analysis on weight based dose response showed that no dose adjustment is required according to weight (as reflected in the SmPC) and is deemed not relevant for the decision problem (please see study report 214861 for more details).

Table 49 List of completed meta-analyses on the mepolizumab trial data

Trial no. (acronym)	Studies included	Primary study ref. (publication)	Inclusion in submission
Meta-analysis of exacerbations requiring hospitalisation or	DREAM, MENSA, SIRIUS, Halder et al.	204664 (Pavord, Ortega H, Keene O, Mayer B, Yancey S. A Meta-Analysis of Exacerbations	Section 4.9.2

hospitalisation/emergency department visit		Requiring Hospitalisation from Studies of Mepolizumab in Severe Eosinophilic Asthma. American Thoracic Society (ATS), Denver, CO, USA, May 15–20, 2015)[134]	
Meta-analysis of clinical efficacy of exacerbation studies	DREAM MENSA	204664 (Integrated Summary of Efficacy Report)	Section 4.9.3
Meta-analysis comparing mepolizumab and omalizumab	Mepolizumab and omalizumab studies	200227 (Integrated Treatment Comparison Report)	See ITC section 4.10
Meta-analysis of mepolizumab weight-based dose response	DREAM MENSA	214861 Austin D, Pouliquen I, Gunsoy N.	Not included – details available in Study Report.

4.9.2 Meta-analysis of exacerbations requiring hospitalisation or hospitalisation/emergency room visit

This analysis studied exacerbations requiring hospitalisation or hospitalisation/emergency department using data from studies DREAM, MENSA, SIRIUS and Haldar 2009. The ITT studies have been too small to provide accurate estimates of the rare hospitalisations and emergency department visit events. By combining the ITT population data of these above four studies, a more robust estimate can be obtained. A detailed summary of the meta-analysis in form of the submitted publication (awaiting review for publication) is attached in the appendix.

The meta-analysis was conducted according to PRISMA statement, based on a defined review protocol.[135] The ITT population was analysed, comprising of all randomised patients who received at least one dose of study medication. Exacerbations included in the analysis were those reported from the start of treatment until completion of study or up to withdrawal (but ≤4 weeks after the last dose of study medication). Asthma exacerbations were considered the same event if separated by less than 7 days. Intensive care unit admission and intubation were included under hospitalisation.
All mepolizumab doses were combined for analysis and compared with placebo as previous studies have shown no difference in the reduction of exacerbations based on a 10-fold dose range of mepolizumab or by a route of administration.[36,136] A pre-specified sensitivity analysis was carried out using the comparable doses of mepolizumab of 75 mg IV and 100 mg SC.

<u>The primary endpoints of this meta-analysis were:</u>
1) annual rate of exacerbations requiring hospitalisation
2) annual rate of exacerbations requiring a hospitalisation and/or an emergency room visit.
The proportion of patients with ≥1 exacerbation requiring hospitalisation and the proportion of patients with ≥1 exacerbation requiring hospitalisation/emergency

department visit were also assessed, not discussed below. A draft publication is available on request from GSK.

Sensitivity analysis was performed excluding the SIRIUS study as it was primarily an oral-sparing study and excluding Haldar 2009 as the study only included the 750 mg IV dose. The inclusion criteria for DREAM, MENSA, SIRIUS and Haldar 2009 were similar. However there were some differences as follows: Haldar 2009 only included adults (≥18 years) and used sputum eosinophils to define eosinophilic asthma whereas DREAM, MENSA and SIRIUS included patients aged ≥12 years; DREAM, MENSA and Haldar 2009 only included patients with ≥2 exacerbations requiring corticosteroid treatment in the previous year, whereas SIRIUS required use of maintenance OCS; definition of eosinophilic asthma in DREAM was not confined to peripheral blood eosinophil levels. Thus, while it may have been appropriate to combine the data for this meta-analysis to get a better understanding of hospitalisation or hospitalisation/emergency department rates, not all individual studies were appropriate for the discussion of the decision problem (Section 4.2). Across all studies, 1388 patients received either mepolizumab IV (75 mg, 250 mg or 750 mg), mepolizumab SC (100 mg), or placebo approximately every 4 weeks as add on therapy to their baseline standard of care (high-dose inhaled corticosteroids and additional asthma controller[s]).

Baseline demographics of the patients in these studies were comparable. The mean age of the patients in each study was approximately 50 years, with a mean asthma duration of 17–24 years. Baseline blood eosinophil counts were similar across all studies (with geometric means ranging 230 to 350 cells/μL), and the mean number of severe exacerbations in the previous year ranged between 2.9 and 5.5. Five hundred out of 1388 (36%) of patients were on maintenance OCS at the start of the studies.

Exacerbations requiring hospitalisation and/or an emergency department visit were significantly reduced by [redacted] Similarly, there was a significant reduction in exacerbations requiring hospitalisation by [redacted] for patients on mepolizumab (all doses pooled, ITT population), compared with placebo (Figure 16).

Figure 16 Meta-analysis of rate of exacerbations requiring hospitalisation or hospitalisation/emergency department visit for all doses of mepolizumab versus placebo.

A sensitivity analysis of mepolizumab 75 mg IV /100 mg SC pooled doses confirmed a significant reduction of [redacted] in hospitalisation/emergency department visit rates and [redacted] in hospitalisation rates, compared with placebo (Figure 17). In all the analyses, the results were consistent between individual studies, with no heterogeneity shown for each outcome across the studies [redacted]

Figure 17 Meta-analysis of rate of exacerbations requiring hospitalisation or hospitalisation/emergency department visit for 75 mg IV/100 mg SC (pooled) doses of mepolizumab versus placebo.

Figure 18 Kaplan-Meier cumulative incidence curve for time to first exacerbation requiring A) hospitalisation; B) hospitalisation and/or emergency department visit.

The sensitivity analysis for patients on the pooled 75 mg IV/100 mg SC doses of mepolizumab showed a reduction of [redacted] for hospitalisation/emergency department visits and [redacted] for hospitalisation, compared with placebo. This trend was confirmed by reduced times to first exacerbation both for first exacerbation requiring hospitalisation or emergency department visit and first exacerbation requiring hospitalisation (Kaplan-Meier curves, Figure 18).

This study had several strengths. All studies included were randomised, placebo-controlled studies. The design of the meta-analysis meant that individual patient level

data was available for all studies included. There was low heterogeneity in the outcomes between the individual studies. All studies in this meta-analysis included patients with severe refractory eosinophilic asthma.

However, the meta-analysis had some limitations. The inclusion criteria, design and doses and posolgies in the four studies were not consistent. Moreover, the analysis included SIRIUS, a steroid sparing study. Unlike MENSA, DREAM and Haldar 2009 looking at spontaneous exacerbation rates, the reduction in steroid dose in SIRIUS could have been a potential trigger of exacerbations.

The maximum duration of treatment with mepolizumab was 1 year. Despite this short duration, the number of patients with ≥1 exacerbation requiring hospitalisation and/or emergency room visit each year was reduced by [redacted] As already mentioned in section 4.7, any reduction in exacerbations is a major benefit to patients and health care services; exacerbations associated with hospitalisation are the severest form of these events, and are associated with considerable morbidity and mortality as well as a long term risk of accelerated lung function decline.[118-120]

4.9.3 Meta-analysis of clinical efficacy of exacerbation studies DREAM and MENSA

4.9.3.1 Methods

A meta-analysis was conducted for the EMA of the two placebo-controlled Exacerbation Studies of similar design, DREAM and MENSA. While both studies included patients with severe refractory eosinophilic asthma and had many similarities in study design, there were differences in eosinophilic inflammation inclusion criteria (see Section 4.3), in the duration of the studies (52 weeks for DREAM and 32 weeks for MENSA) and in the doses and route of administration of mepolizumab.

Outcome measures

The following efficacy endpoints have been combined for this meta-analysis; these endpoints represent the key endpoints that were collected in both studies:
Exacerbation endpoints:

- Rate of clinically significant asthma exacerbations
- Rate of clinically significant exacerbations requiring hospitalisation and/or ED visits
- Rate of clinically significant exacerbations that led to hospitalisation
- Lung function endpoints: Mean change from baseline in pre- and post-bronchodilator FEV_1

Other endpoints:

- Mean change from baseline in ACQ score – symptoms only
- Subject and clinician rating of overall response to therapy

Statistical analysis

Complete details of the meta-analyses performed for this Efficacy Summary document can be found in the Efficacy Summary Document Analysis Plan

[GlaxoSmithKline Document Number 2014N189767_00], located in the Reference Pack.
Meta-analysis of DREAM and MENSA used the Intent-to-Treat (ITT) Population consisting of all randomised subjects who received at least one dose of study medication. Whilst this analysis has not been undertaken for the proposed population it does provide a useful context to the generalisability of the results from MENSA to the evidence base including DREAM.

The following treatment comparisons (see Section 2.2) were performed:

- 75 mg IV vs. Placebo
- 75 mg IV+100 mg SC vs. Placebo
- All mepolizumab doses combined vs. Placebo

Subgroup and Covariate Definitions:
For the meta-analysis of the data from DREAM and MENSA subgroups were defined as follows:

- Age: 12 to 17, 18 to 64, ≥65 years
- Gender: Male, Female
- Race: African American/African Heritage, White, Asian, Other
- Baseline Blood Eosinophils: <150, ≥150 to <300, ≥300 to <500, ≥500 cells/μL
- Geographical Region: United States, European Union, Rest of World (Where European Union includes Belgium, France, Germany, Italy, Poland, Romania, Spain, and the United Kingdom (UK), and Rest of World includes Argentina, Australia, Canada, Chile, Japan, Korea, Mexico, Russia, and Ukraine).
- Weight: ≤60, >60 to ≤75, >75 to ≤90, >90 kg

The rate of clinically significant exacerbations was analysed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable) and baseline percent predicted pre-bronchodilator FEV_1, with logarithm of time on treatment as an offset variable. 'Study' was included as a covariate in the meta-analysis.

For the meta-analysis, the model estimated mean rate per year for each treatment was based on a weighting being applied to each level of the class variables in the model, the weightings being determined from observed proportions.

There was no predefined order of importance in the analysis of endpoints and no formal adjustments for multiplicity were applied.

4.9.3.2 Results

The meta-analysis of DREAM and MENSA allows a comparison of the combined 75 mg IV+100 mg SC and all mepolizumab doses combined data versus the GSK proposed population and ITT data presented in section 4.7. The ITT population results for MENSA, DREAM and combined results are presented below.

Patient demographics

Table 50 Comparing DREAM and MENSA and Meta-Analysis Demographic Characteristics (ITT Population)

	Placebo N=346	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=344	Mepolizumab 75 mg IV/ 100 mg SC[1] N=538	Mepolizumab All Doses[2] N=846	Total N=1192
DREAM						
N	155		153		461	616
Gender, N (%)						
Female	97 (63)		104 (68)		290 (63)	387 (63)
Male	58 (37)		49 (32)		171 (37)	229 (37)
Age (yr)						
Mean (SD)	46.4 (11.33)		50.2 (10.84)		49.4 (11.18)	48.6 (11.28)
Min, Max	20,68		23,69		15, 74	15, 74
Age Group, n (%)						
12-17 years old	0		0		1(<1)	1 (<1)
18-64 years old	150 (97)		144 (94)		440 (95)	590 (96)
≥65 years old	5 (3)		9 (6)		20 (4)	25 (4)
65-74 years old	5 (3)		9 (6)		20 (4)	25 (4)
Race Category, n (%)						
African American/African Heritage	6 (4)		5 (3)		17 (4)	23 (4)
American Indian or Alaskan Native	0		1 (<1)		2(<1)	2 (<1)
Asian	9 (6)		9 (6)		26 (6)	35 (6)
Native Hawaiian or other Pacific Islander	0		0		0	0
White	140 (90)		138 (90)		414 (90)	554 (90)
African American/African Heritage & White	0		0		1(<1)	1 (<1)
American Indian or Alaskan native & White	0		0		0	0
Asian & native Hawaiian or Other Pacific Islander	0		0		1(<1)	1(<1)
Asian & White	0		0		0	0
Ethnicity, n (%)						
Hispanic/Latino	16 (10)		16 (10)		46 (10)	62 (10)
Not Hispanic/Latino	139 (90)		137 (90)		415 (90)	554 (90)
Body mass Index (kg/m^2)						
Mean (SD)	28.26 (6.121)		28.42 (5.965)		28.54 (5.897)	28.47 (5.950)
Min, Max	18.8, 52.2		17.6, 48.3		17.4, 49.5	17.4, 52.2
MENSA						
N	191	194	191	385	385	576
Gender, N (%)						
Female	107 (56)	116 (60)	105 (55)	221 (57)	221 (57)	328 (57)
Male	84 (44)	78 (40)	86 (45)	164 (43)	164 (43)	248 (43)
Age (yr)						
Mean (SD)	49.2 (14.26)	51.2 (14.55)	50.0 (14.03)	50.6 (14.29)	50.6 (14.29)	50.1 (14.28)
Min, Max	12, 76	12, 81	13, 82	12, 82	12, 82	12, 82

Age Group, n (%)						
12-17 years old	9 (5)	7 (4)	9 (5)	16 (4)	16 (4)	25 (4)
18-64 years old	156 (82)	157 (81)	158 (83)	315 (82)	315 (82)	471 (82)
≥65 years old	26 (14)	30 (15)	24 (13)	54 (14)	54 (14)	80 (14)
65-74 years old	23 (12)	22 (11)	20 (10)	42 (11)	42 (11)	65 (11)
75-84 year old	3 (2)	8 (4)	4 (2)	12 (3)	12 (3)	15 (3)
Race Category, n (%)						
African American/ African Heritage	3 (2)	7 (4)	6 (3)	13 (3)	13 (3)	16 (3)
American Indian or Alaskan Native	0	1 (<1)	0	1 (<1)	1 (<1)	1 (<1)
Asian	38 (20)	34 (18)	34 (18)	68 (18)	68 (18)	106 (18)
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0
White	148 (77)	152 (78)	150 (79)	302 (78)	302 (78)	450 (78)
African American/ African Heritage & White	1 (<1)	0	0	0	0	1 (<1)
American Indian or Alaskan native & White	0	0	1 (<1)	1 (<1)	1 (<1)	1(<1)
Asian & native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
Asian & White	1 (<1)	0	0	0	0	1(<1)
Ethnicity, n (%)						
Hispanic/Latino	15 (8)	18 (9)	18 (9)	36 (9)	36 (9)	51 (9)
Not Hispanic/Latino	176 (92)	176 (91)	173 (91)	349 (91)	349 (91)	525 (91)
Body mass Index (kg/m^2)						
Mean (SD)	28.04 (5.588)	27.60 (6.214)	27.68 (5.682)	27.64 (5.948)	27.64 (5.948)	27.77, 5.830
Min, Max	17.7, 49.7	17.0, 49.5	16.1, 45.9	16.1, 49.5	16.1, 49.5	16.1, 49.7
DREAM & MENSA						
N	346		344	538	846	1192
Gender, N (%)						
Female	204 (59)		209 (61)	325 (60)	511 (60)	715 (60)
Male	142 (41)		135 (39)	213 (40)	335 (40)	477 (40)
Age (yr)						
Mean (SD)	47.9 (13.08)		50.1 (12.70)	50.5 (13.9)	49.9 (12.70)	49.3 (12.83)
Min, Max	12, 76		13, 82	12, 82	12, 82	12, 82
Age Group, n (%)						
12-17 years old	9 (3)		9 (3)	16 (3)	17 (2)	26 (2)
18-64 years old	306 (88)		302 (88)	459 (85)	755 (89)	1061 (89)
≥65 years old	31 (9)		33 (10)	63 (12)	74 (9)	105 (9)
65-74 years old	28 (8)		29 (8)	51 (9)	62 (7)	90 (8)
75-84 year old	3 (<1)		4 (1)	12 (2)	12 (1)	15 (1)

There were no notable differences in demographics when combining data in the meta-analysis compared the individual trial ITT populations or GSK proposed population (apart from the demographics selected to be different in this more severe population); please see section 4.5 and 4.13 for more detail and discussion.

Table 51 Summary of History of Asthma Exacerbations in the Previous Year (DREAM, MENSA and Meta-Analysis, ITT Population)

	Placebo N=346	Mepolizumab 100 mg SC	Mepolizumab 75 mg IV	Mepolizumab 75 mg IV/100 mg	Mepolizumab All Doses[2]	Total N=1192

		N=194	N=344	SC[1] N=538	N=846	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
DREAM						
Total number of exacerbations						
n	155		153		461	616
0	0		0		0	0
1	1 (<1)		0		1 (<1)	2 (<1)
2	65 (42)		70 (46)		219 (48)	284 (46)
>2	89 (57)		83 (54)		241 (52)	330 (54)
Asthma exacerbations requiring ED visit and/or hospitalisation						
n	155		153		461	616
0	84 (54)		90 (59)		261 (57)	345 (56)
1	28 (18)		30 (20)		79 (17)	107 (17)
2	26 (17)		23 (15)		79 (17)	105 (17)
>2	17 (11)		10 (7)		42 (9)	59 (10)
Asthma exacerbations requiring hospitalisation						
n	155		153		461	616
0	115 (74)		118 (77)		351 (76)	466 (76)
1	19 (12)		25 (16)		68 (15)	87 (14)
2	15 (10)		9 (6)		32 (7)	47 (8)
>2	6 (4)		1 (<1)		10 (2)	16 (3)
MENSA						
Total number of exacerbations						
n	191	194	191	385	385	576
0	0	0	0	0	0	0
1	1 (<1)	0	0	0	0	1 (<1)
2	89 (47)	74 (38)	82 (43)	156 (41)	156 (41)	245 (43)
>2	101 (53)	120 (62)	109 (57)	229 (59)	229 (59)	330 (57)
Asthma exacerbations requiring ED visit and/or hospitalisation						
n	191	194	191	385	385	576
0	127 (66)	129 (66)	130 (68)	259 (67)	259 (67)	386 (67)
1	30 (16)	29 (15)	30 (16)	59 (15)	59 (15)	89 (15)
2	19 (10)	17 (9)	17 (9)	34 (9)	34 (9)	53 (9)
<2	15 (8)	19 (10)	14 (7)	33 (9)	33 (9)	48 (8)
Asthma exacerbations requiring hospitalisation						
n	191	194	191	385	385	576
0	156 (82)	161 (83)	150 (79)	311 (81)	311 (81)	467 (81)
1	18 (9)	16 (8)	29 (15)	45 (12)	45 (12)	63 (11)
2	7 (4)	10 (5)	10 (5)	20 (5)	20 (5)	27 (5)
>2	10 (5)	7 (4)	2 (1)	9 (2)	9 (2)	19 (3)
DREAM & MENSA						
Total number of exacerbations						
n	346		344	538	846	1192
0	0		0	0	0	0
1	2 (<1)		0	0	1 (<1)	3 (<1)
2	154 (45)		152 (44	226 (42)	375 (44)	529 (44)
>2	190 (55)		192 (56)	312 (58)	470 (56)	660 (55)
Asthma exacerbations requiring ED visit and/or hospitalisation						
n	346		344	538	846	1192
0	211 (61)		220 (64)	349 (65)	520 (61)	731 (61)
1	58 (17)		60 (17)	89 (17)	138 (16)	196 (16)
2	45 (13)		40 (12)	57 (11)	113 (13)	158 (13)
>2	32 (9)		24 (7)	43 (8)	75 (9)	107 (9)
Asthma exacerbations requiring hospitalisation						
n	346		344	538	846	1192
0	271 (78)		268 (78)	429 (80)	662 (78)	933 (78)
1	37 (11)		54 (16)	70 (13)	113 (13)	150 (13)
2	22 (6)		19 (6)	29 (5)	52 (6)	74 (6)
>2	16 (5)		3 (<1)	10 (2)	19 (2)	35 (3)

Rate of exacerbations

Table 52 Analysis of Rate of Clinically Significant Exacerbations (DREAM, MENSA and Meta-Analysis, ITT Population)

Rate of Clinically Significant Exacerbations	Placebo N=346	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=344	Mepolizumab 75 mg IV/ 100 mg SC[4] N=538	Mepolizumab All Doses5 N=846
DREAM					
n	155		153		461
Exacerbation rate/year	2.40		1.24		1.28
Comparison vs. placebo[1]					
Rate ratio (mepolizumab/placebo)	---		0.52		0.53
(95% CI)	---		(0.39, 0.69)		(0.43, 0.67)
p-value	---		<0.001		<0.001
MENSA					
n	191	194	191	385	385
Exacerbation rate/year	1.75	0.81	0.93	0.87	0.87
Comparison vs. placebo[2]					
Rate ratio (mepolizumab/placebo)	---	0.47	0.53	0.50	0.50
(95% CI)	---	(0.35, 0.63)	(0.39, 0.71)	(0.39, 0.64)	(0.39, 0.64)
p-value	---	<0.001	<0.001	<0.001	<0.001
DREAM & MENSA					
n	346		344	538	846
Exacerbation rate/year	1.91		1.00	0.97	1.00
Comparison vs. placebo[3]					
Rate ratio (mepolizumab/placebo)	---		0.52	0.51	0.52
(95% CI)	---		(0.42, 0.64)	(0.42, 0.61)	(0.44, 0.62)
p-value	---		<0.001	<0.001	<0.001

1. Analysis performed using a negative binomial regression model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable), and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. 2. Analysis model as in footnote [1]; estimates based on weighting applied to each level of class variable determined from observed proportions. 3. Analysis model as in footnote [2] where region is as defined for the meta-analysis and with an additional covariate of study. 4. For DREAM, the 75 mg IV/100 mg SC grouping is the same as the 75 mg IV grouping, since DREAM does not include a 100 mg SC dose. 5. DREAM includes 75, 250, and 750 mg IV. MENSA includes 75 mg IV and 100 mg SC; therefore, the All Doses grouping is the same as the 75 mg IV/100 mg SC grouping. DREAM+MENSA include 75, 250, and 750 mg IV and 100 mg SC.

Results of the meta-analysis demonstrated similar reductions in the rate of clinically significant exacerbations (49% for mepolizumab 75 mg IV+100 mg SC) to the mepolizumab 100 mg SC dose in MENSA (53%). This compares to the GSK proposed population where a similar reduction (50%) compared to the combined 75 mg IV+100 mg SC data was demonstrated.

Table 53 Analysis of Rate of Clinically Significant Exacerbations by Baseline Blood Eosinophils (Meta-Analysis of DREAM and MENSA, ITT Population)

	Placebo N=346	Mepolizumab 75 mg IV/100 mg SC[2] N=538	Mepolizumab All Doses[3] N=846
DREAM + MENSA			
<150 cells/µL			
n	66	123	199
Exacerbation rate/year	1.73	1.16	1.28
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo)	---	0.67	0.74
(95% CI)	---	(0.46, 0.98)	(0.52, 1.04)

150 to <300 cells/µL			
n Exacerbation rate/year	86 1.41	139 1.01	224 0.95
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo) (95% CI)	--- ---	0.72 (0.47, 1.10)	0.67 (0.45, 1.01)
300 to <500 cells/µL			
n Exacerbation rate/year	76 1.64	109 1.02	180 1.06
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo) (95% CI)	--- ---	0.62 (0.41, 0.93)	0.64 (0.45, 0.92)
≥500 cells/µL			
n Exacerbation rate/year	116 2.49	162 0.67	238 0.75
Comparison vs. placebo[1]			
Rate ratio (mepolizumab/placebo) (95% CI)	--- ---	0.27 (0.19, 0.37)	0.30 (0.23, 0.40)

1. Analysis performed using a negative binomial regression model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable), baseline % predicted FEV1, and study, with logarithm of time on treatment as an offset variable.
Estimates based on weighting applied to each level of class variable determined from observed proportions.
Region was as defined for the Efficacy Summary.
2. Only MEA115588 includes 100 mg SC dose.
3. Includes 75, 250, and 750 mg IV and 100 mg SC
MEA112997 = DREAM, MEA115588 = MENSA

DREAM's inclusion criteria were not only based on blood eosinophil levels but allowed subjects to enter the trial on 4 separate criteria (see section 4.3). MENSA on the other hand, used the inclusion criteria identified by multivariate modelling of DREAM data. Thus, MENSA only included appropriate patients that were identified as responders to add-on mepolizumab therapy in DREAM. This may explain the differences seen in clinically significant exacerbations by screening blood eosinophils between DREAM and MENSA (Figure 12, Figure 13 Section 4.8) as well as the less specific reduction in rate of exacerbations based on eosinophil levels when pooling these two data sets in Table 53.

Exacerbations Requiring Emergency Department Visits and/or Hospitalisation

Table 54 Analysis of Rate of Exacerbations Requiring Hospitalisation/ED Visits (DREAM, MENSA and Meta-Analysis, ITT Population)

Rate of Exacerbations Requiring Hospitalisation/ED Visits	Placebo N=346	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=344	Mepolizumab 75 mg IV/ 100 mg SC[4] N=538	Mepolizumab All Doses[5] N=846
DREAM					
n Exacerbation rate/year	155 0.43		153 0.17		461 0.22
Comparison vs. placebo[1]					
Rate ratio (mepolizumab/placebo)	----		0.40		0.50

(95% CI)	----		(0.19, 0.81)		(0.29, 0.85)
p-value	----		0.011		0.011
MENSA					
n	191	194	191	385	385
Exacerbation rate/year	0.20	0.08	0.14	0.11	0.11
Comparison vs. placebo[2]					
Rate ratio (mepolizumab/placebo)	----	0.39	0.68	0.52	0.52
95% CI	----	(0.18, 0.83)	(0.33, 0.41)	(0.28, 0.96)	(0.28, 0.96)
p-value	----	0.015	0.299	0.037	0.037
DREAM & MENSA					
n	346		344	538	846
Exacerbation rate/year	0.26		0.15	0.14	0.16
Comparison vs. placebo[3]					
Rate ratio (mepolizumab/placebo)	----		0.58	0.53	0.60
(95% CI)	----		(0.35, 0.97)	(0.33, 0.84)	(0.40, 0.89)
p-value	----		0.037	0.007	0.012

1. Analysis performed using a negative binomial regression model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable), and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. 2. Analysis model as in footnote [1]; estimates based on weighting applied to each level of class variable determined from observed proportions. 3. Analysis model as in footnote [2] where region is as defined for the meta-analysis and with an additional covariate of study. 4. For DREAM, the 75 mg IV/100 mg SC grouping is the same as the 75 mg IV grouping, since DREAM does not include a 100 mg SC dose.
5. DREAM includes 75, 250, and 750 mg IV. MENSA includes 75 mg IV and 100 mg SC; therefore, the All Doses grouping is the same as the 75 mg IV/100 mg SC grouping. DREAM+MENSA include 75, 250, and 750 mg IV and 100 mg SC.

Table 55 Analysis of Rate of Exacerbations Requiring Hospitalisation (DREAM, MENSA and Meta-Analysis, ITT Population)

Rate of Exacerbations Requiring Hospitalisation	Placebo N=346	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=344	Mepolizumab 75 mg IV/ 100 mg SC[4] N=538	Mepolizumab All Doses[5] N=846
DREAM					
n	155		153		461
Exacerbation rate/year	0.18		0.11		0.10
Comparison vs. placebo[1]					
Rate ratio (mepolizumab/placebo)	----		0.61		0.54
(95% CI)	----		(0.28, 1.33)		(0.29, 1.00)
p-value	----		0.214		0.051
MENSA					
n	191	194	191	385	385
Exacerbation rate/year	0.10	0.03	0.06	0.05	0.05
Comparison vs. placebo[2]					
Rate ratio (mepolizumab/placebo)	----	0.31	0.61	0.44	0.44
95% CI	----	(0.11, 0.91)	(0.23, 1.66)	(0.19, 1.02)	(0.19, 1.02)
p-value	----	0.034	0.334	0.056	0.056
DREAM & MENSA					
n	346		344	538	846
Exacerbation rate/year	0.14		0.08	0.07	0.07
Comparison vs. placebo[3]					
Rate ratio (mepolizumab/placebo)	----		0.57	0.50	0.49
(95% CI)	----		(0.31, 1.06)	(0.28, 0.89)	(0.30, 0.81)
p-value	----		0.076	0.018	0.005

1. Analysis performed using a negative binomial regression model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable), and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. 2. Analysis model as in footnote [1]; estimates based on weighting applied to each level of class variable

determined from observed proportions. 3. Analysis model as in footnote [2] where region is as defined for the meta-analysis and with an additional covariate of study 4. For DREAM, the 75 mg IV/100 mg SC grouping is the same as the 75 mg IV grouping, since DREAM does not include a 100 mg SC dose. 5. DREAM includes 75, 250, and 750 mg IV. MENSA includes 75 mg IV and 100 mg SC; therefore, the All Doses grouping is the same as the 75 mg IV/100 mg SC grouping. DREAM+MENSA include 75, 250, and 750 mg IV and 100 mg SC.

Results of the meta-analysis demonstrated similar reductions in the rate of exacerbations requiring ED visits and/or hospitalisation for mepolizumab 75 mg IV+100 mg SC to that observed in MENSA and the GSK proposed population (section 4.7).

The rate of events of ED visits and/or hospitalisation is small and thus it is difficult to draw robust conclusion from this data. Nevertheless, the fact that the results were consistent across the meta-analysis and the individual ITT results, this supports the generalisability of the results from MENSA to the broader evidence base.

Asthma Control Questionnaire

Table 56 Analysis of Change from Baseline in ACQ Symptoms (DREAM, MENSA and Meta-Analysis, ITT Population)

ACQ	Placebo N=346	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=344	Mepolizumab 75 mg IV/ 100 mg SC[2] N=538	Mepolizumab All Doses[3] N=846
DREAM					
n[1] at Week 32	152		149		450
n[2] at Week 32	128		132		398
LS Mean	1.74		1.61		1.60
LS Mean Change (SE for mean and mean change)	-0.64 (0.088)		-0.77 (0.088)		-0.79 (0.054)
Comparison vs. placebo[1]					
Difference (mepolizumab/placebo)	----		-0.13		-0.15
(95% CI)	----		(-0.36, 0.10)		(-0.34, 0.04)
p-value	----		0.278		0.129
n[1] at Week 52	152		149		450
n[2] at Week 52	121		125		375
LS Mean	1.75		1.60		1.53
LS Mean Change (SE for mean and mean change)	-0.63 (0.092)		-0.78 (0.091)		-0.85 (0.056)
Comparison vs. placebo[1]					
Difference (mepolizumab/placebo)	----		-0.15		-0.22
(95% CI)	----		(-0.39, 0.10)		(-0.42, -0.02)
p-value	----		0.232		0.032
MENSA					
n[1] at Week 32	184	189	179	368	368
n[2] at Week 32	170	173	161	334	334
LS Mean	1.70	1.26	1.28	1.27	1.27
LS Mean Change (SE for mean and mean change)	-0.50 (0.069)	-0.94 (0.068)	-0.92 (0.070)	-0.93 (0.049)	-0.93 (0.049)
Comparison vs. placebo[1]					

Difference (mepolizumab/placebo)	----	-0.44	-0.42	-0.43	-0.43
(95% CI)	----	(-0.63, -0.25)	(-0.61, -0.23)	(-0.59, -0.26)	(-0.59, -0.26)
p-value	----	<0.001	<0.001	<0.001	<0.001
DREAM & MENSA					
N [1] at Week 32	336		328	517	818
n [2] at Week 32	298		292	465	732
LS Mean	1.77		1.47	1.43	1.48
LS Mean Change	-0.55		-0.84	-0.88	-0.84
(SE for Mean and Mean Change)	(0.054)		(0.055)	(0.045)	(0.035)
Comparison vs. Placebo[1]					
Difference (mepolizumab/placebo)	---		-0.29	-0.34	-0.29
(95% CI)	---		(-0.45, -0.14)	(-0.48, -0.20)	(-0.42, -0.17)
p-value	---		<0.001	<0.001	<0.001

1. Analysis performed using mixed model repeated measures with covariates of baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), baseline % predicted FEV_1, exacerbations in the year prior to the study (as an ordinal variable), treatment, and visit, plus interaction terms for visit by baseline and visit by treatment group. Estimates for MENSA and DREAM+MENSA are based on weighting applied to each level of class variable determined from observed proportions. For the individual studies, region is as defined in the study. For the DREAM+MENSA meta-analysis, region is as defined for the meta-analysis and study is included as a covariate.
2. For DREAM, the 75 mg IV/100 mg SC grouping is the same as the 75 mg IV grouping, since DREAM does not include a 100 mg SC dose.
3. DREAM includes 75, 250, and 750 mg IV. MENSA includes 75 mg IV and 100 mg SC; therefore, the All Doses grouping is the same as the 75 mg IV/100 mg SC grouping. DREAM+MENSA include 75, 250, and 750 mg IV and 100 mg SC.
Note: The ACQ-6 was used in DREAM. The ACQ-5 was used in MENSA. For the meta-analysis, only questions regarding symptoms collected in both studies were used to calculate a symptom score.
Note: n [1]=number of subjects with analyzable data for one or more time points; n [2]=number of subjects with analyzable data at the given time point

Results of the meta-analysis of mepolizumab 75 mg IV+100 mg SC and mepolizumab 75 mg IV showed similar improvements in ACQ symptoms from baseline at Week 32 compared with placebo (-0.34, and -0.29 points, respectively; p<0.001 for each) to that observed with the mepolizumab 100 mg SC dose in MENSA (section 4.7).

Pre-Bronchodilator FEV_1

Table 57 Analysis of Change from Baseline in Pre-Bronchodilator FEV_1 (mL) (DREAM, MENSA and Meta-Analysis, ITT Population)

FEV_1	Placebo N=346	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=344	Mepolizumab 75 mg IV/ 100 mg SC[2] N=538	Mepolizumab All Doses[3] N=846
DREAM					
Week 32					
n[1] at Week 32	154		152		459
n[2] at Week 32	134		136		412
LS Mean	2021		2024		1989
LS Mean change (SE for mean and mean change)	139 (37.6)		142 (37.6)		107 (23.1)
Comparison vs. placebo[1]					
Difference (mepolizumab/placebo)	----		3		-32
(95% CI)	----		(-97, 102)		(-114, 49)
p-value	----		0.958		0.436
Week 52					

n[1] at Week 52 n[2] at Week 52 LS Mean LS Mean change (SE for mean and mean change)	154 127 1942 60 (37.7)		152 129 2003 121 (37.6)		459 390 2008 126 (23.0)
Comparison vs. placebo[1]					
Difference (mepolizumab/placebo) (95% CI) p-value	---- ---- ----		61 (-39, 161) 0.229		66 (-15, 147) 0.112
MENSA					
Week 32					
n[1] at Week 32 n[2] at Week 32 LS Mean LS Mean change (SE for mean and mean change)	189 179 1907 86 (31.4)	192 185 2005 183 (31.1)	188 176 2007 186 (31.5)	380 361 2006 184 (22.1)	380 361 2006 184 (22.1)
Comparison vs. placebo[1]					
Difference (mepolizumab/placebo) (95% CI) p-value	---- ---- ----	98 (11, 184) 0.028	100 (13, 187) 0.025	99 (23, 174) 0.010	99 (23, 174) 0.010
DREAM & MENSA					
Week 32					
n[1] at Week 32 n[2] at Week 32 LS Mean LS Mean change (SE for mean and mean change)	343 313 1967 107 (23.8)		340 312 2023 163 (23.9)	532 497 2029 169 (19.8)	839 773 2001 141 (15.1)
Comparison vs. placebo[1]					
Difference (mepolizumab/placebo) (95% CI) p-value	--- --- ---		56 (-10, 122) 0.094	63 (3, 123) 0.040	37 (-18, 92) 0.189

1. Analysis performed using mixed model repeated measures with covariates of baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbations in the year prior to the study (as an ordinal variable), treatment, and visit, plus interaction terms for visit by baseline and visit by treatment group. Estimates for MENSA and DREAM+MENSA are based on weighting applied to each level of class variable determined from observed proportions. For the individual studies, region is as defined in the study. For the DREAM+MENSA meta-analysis, region is as defined for the meta-analysis and study is included as a covariate.
2. For DREAM, the 75 mg IV/100 mg SC grouping is the same as the 75 mg IV grouping, since DREAM does not include a 100 mg SC dose.
3. DREAM includes 75, 250, and 750 mg IV. MENSA includes 75 mg IV and 100 mg SC; therefore, the All Doses grouping is the same as the 75 mg IV/100 mg SC grouping. DREAM+MENSA includes 75, 250, and 750 mg IV and 100 mg SC.
Note: n [1]=number of subjects with analyzable data for one or more time points; n [2]=number of subjects with analyzable data at the given time point

Results of the meta-analysis showed a smaller improvement in pre-bronchodilator FEV_1 from baseline to Week 32 compared to the mepolizumab 100 mg SC dose in MENSA (section 4.7.5.5)

4.9.3.3 Summary

This meta-analysis of two placebo-controlled exacerbation studies (DREAM & MENSA) ranging from 32 to 52 weeks duration showed results that were comparable to the individual ITT population. When comparing the meta-analysis results to the GSK proposed population, asthma control (ACQ) showed a greater improvement in

the GSK proposed population. Indeed, in the GSK proposed population the improvement in ACQ reached clinical significance in contrary to the ITT population.

Exacerbations, including those requiring emergency department visits and/or hospitalisation were comparable to the reduction observed in the GSK proposed population. However, the comparison of emergency department visits and/or hospitalisation should be made with caution as the rate of these events is generally low making it difficult to draw any conclusions.

This study has several strengths. All studies included were randomised, placebo-controlled studies. The design of the meta-analysis meant that individual patient level data was available for all studies included. There was low heterogeneity in the outcomes between the individual studies. All studies in this meta-analysis included patients with severe refractory eosinophilic asthma.

However, the meta-analysis had some limitations. Firstly, at the request of the EMA this was restricted to the two exacerbation studies only. However given the other studies (e.g. SIRIUS and Halder et al) had major differences in study design and patient population for most endpoint this comparison is of relevance. Since mepolizumab 100 mg SC and 75 mg IV have comparable bioavailability, a comparison based on combining these two treatment groups is presented. However, it should be noted that DREAM was a dose ranging study that also aimed to identify a mepolizumab appropriate responder population (blood eosinophil count);. DREAM patients included subject who did not fulfill the responder criteria taken into phase III clinical trials (blood eosinophil thresholds). The data of DREAM and pooled data of DREAM and MENSA should, therefore, be reviewed in light of this limitation.

A meta-analysis for the GSK proposed population was not performed. However in consideration of the consistent results seen in the individual ITT studies and the meta-analysis, a reasonable assumption can be made that the results of MENSA can be considered representative of the broader evidence base.

4.10 Indirect and mixed treatment comparisons

Add-on omalizumab has been identified as a relevant comparator for add-on mepolizumab in the 'overlap' population i.e. those patients who exhibit both allergic (IgE) and eosinophilic phenotypes of severe asthma and that would be eligible for either medication based on approved or anticipated indication and NICE guidance (see Section 3). From the mepolizumab trials, the percentage overlap i.e. those mepolizumab eligible patients also eligible for omalizumab is estimated at [redacted] There are no head-to-head RCTs directly comparing mepolizumab and omalizumab. Accordingly, a network meta-analysis (NMA) was employed to compare the two treatments indirectly, by synthesising available RCT evidence via a common comparator, standard of care (SoC).

4.10.1 Search strategy

Details of the search strategies and methodology employed to identify relevant clinical data for mepolizumab and omalizumab can be found in Section 4.1 and Appendix 8.7. Note that eligibility into the NMA was based on a previous data cut of the systematic literature review where searches were undertaken on the 8th July 2014 (although the recent update on the 16th July 2015 did not reveal any further studies that would have been included in any subsequent NMAs). In total 29

omalizumab publications and 4 mepolizumab publications (from the 2014 search) (corresponding to 19 and 3 distinct underlying studies respectively) were identified by the clinical effectiveness systematic literature review and were thus available for assessment in order to determine their eligibility for the NMAs.

4.10.2 Study selection

Study design inclusion criteria

Parallel group RCT, double blind study (open label studies included in sensitivity analyses only) with a duration of ≥12 weeks were included. Where a protocol-driven change in ICS/OCS maintenance dosage was implemented, only those data from periods prior to the change were included in the ITC. At least one pre-defined relevant and comparable efficacy or safety endpoint must have been determined, extracted or calculated from the available RCT data. All other study types were excluded such as single arm studies, pre-clinical and Phase I studies. Interventions of interest included SoC, placebo, mepolizumab and omalizumab.

Patient population

The relevant patient population for the NMA was first defined as severe asthma patients, aged ≥12 years of age, receiving ≥ 1,000 mcg/day BDP equivalent plus ≥ 1 additional controller, with a documented history of exacerbations. As mepolizumab and omalizumab are targeted to treat different phenotypes of severe asthma, the most relevant comparison between mepolizumab and omalizumab would include only those patients eligible for both treatments.

We have access to mepolizumab individual patient data (IPD) and hence it is possible to identify patients within the mepolizumab trial dataset who meet the weight, IgE and positive RAST test (based on 4 allergens) criteria for omalizumab eligibility. However, it is not possible to implement the corresponding process of identifying the mepolizumab-eligible subset of the omalizumab dataset, because only aggregate omalizumab RCT data are available at this time. It is also not possible to identify the patients from the omalizumab RCT aggregate data that meet the restrictions of the recent NICE MTA guidance (TA 278) where patients with severe persistent allergic asthma (IgE-mediated) are also required to need continuous or frequent treatment with oral OCS.[137]

It is also worth noting that the RCTs differed substantially with respect to the severity of patients enrolled, according to their exacerbation history. In some omalizumab RCTs no exacerbation history was required at enrolment, while mepolizumab RCTs required a history of two or more asthma exacerbations treated with systemic corticosteroids in the previous 12 months.

Accordingly, in order to assure feasibility, it was necessary to define a minimum exacerbation history inclusion criterion for the NMA that was both strict enough to help identify patients of similar severity (according to exacerbation history), but not so strict as to exclude all omalizumab RCTs from the NMA. Consequently, the distribution of severity (as indicated by exacerbation history) is likely to differ somewhat between the mepolizumab and omalizumab patients included in any

approximated ‘overlap’ analysis in this NMA. GSK considered three alternative approaches to identifying the overlap populations which are presented in Figure 19.

Population 1 ‘overlap’: Omalizumab eligible patients with ≥2 systemic corticosteroid treated exacerbations or hospitalisation / ED exacerbation in the previous 12 months, mepolizumab patients meeting this criteria.

Population 2 ‘extended overlap’: Omalizumab eligible patients with ≥1 systemic corticosteroid treated exacerbations in the previous 12 months, mepolizumab patients meeting this criteria.

Population 3 ‘full trial’: omalizumab eligible patients (as per population 2) and all mepolizumab eligible patients irrespective of whether they are omalizumab eligible with ≥2 systemic corticosteroid treated exacerbations in the previous year.

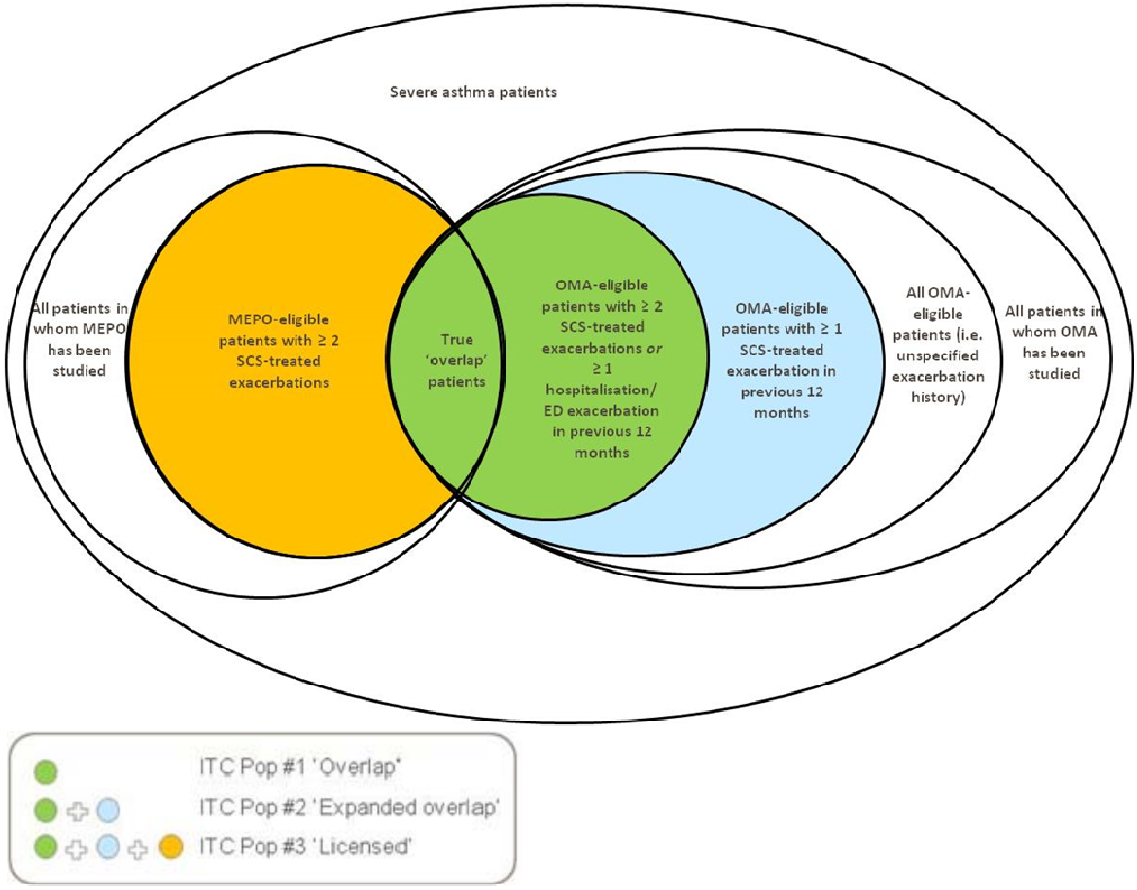
For each of the three populations, 4 scenarios were considered:

1. RCT data only; for mepolizumab pooling both 75mg IV and 100mg SC data
2. RCT data only; for mepolizumab SC data only
3. Addition of open-label RCTs compared with mepolizumab SC data only
4. Addition of open-label RCTs and for mepolizumab pooling both 75mg IV and 100mg SC data.

Figure 19 shows that by relaxing the exacerbation history inclusion criteria, more data become eligible for inclusion in the NMA. Note that the exacerbation history inclusion criteria is the same between populations 2 ‘extended overlap’ and 3 ‘Full trial’. Moving from population 2 ‘extended overlap’ and population 3 ‘Full trial’ shows the expansion of the mepolizumab data set included, in order to try and compare the entire mepolizumab dataset for the target population with omalizumab patients who are likely to have a similar disease severity. None of the populations considered reflect the ‘true’ overlap population since without IPD for omalizumab and using omalizumab aggregate data we have to assume that 100% of the patients contributing to the aggregate data are eligible for mepolizumab which we know not to be the case.

Although population 3 relaxes the requirement for omalizumab eligibility amongst mepolizumab patients we believe it provides a more balanced comparison of the entirety of the data than the estimates of the overlap population which include subsets of the mepolizumab RCT data but population level omalizumab data. Specifically we pool both relevant IV and SC arms from the available mepolizumab RCTs (based on proven bioequivalence (see section 4.7.3.2). For this reason, only the results for population 3 ‘Full trial’ are shared in detail in the main body of the submission and in the base case economic analysis.

Figure 19 Conceptual diagram of the ITC populations 'overlap', 'extended overlap' and 'full trial'



Consideration of eligibility into the NMA

The following criteria were used to assess the eligibility of the mepolizumab and omalizumab RCTs identified from the systematic literature review (see section 4.1)

Mepolizumab eligibility

People with severe eosinophilic asthma who have either a blood eosinophil count of ≥150 cells/μL at initiation of treatment or a blood eosinophil count ≥300 cells/μL in the prior 12 months and with a history of exacerbations. The relevant mepolizumab intervention is defined as 100mg SC or 75mg IV plus SoC. This is in accordance with the trial inclusion criteria for MENSA.

Omalizumab eligibility

Patients had to have allergic asthma, i.e. demonstrated a positive skin test for any of four specified aeroallergens plus a baseline IgE level ≥ 30 IU/mL to ≤ 1,500 IU/mL and weighed between ≥ 20 kg to <150 kg. Maximum dosage of 600 mg SC every 2 weeks. This is in accordance with the SmPC.[138]

Outcomes of interest

Prior to feasibility assessment, a range of pre-specified primary (exacerbation related) and secondary (HRQL, lung function, asthma control and safety) endpoints were considered based on those included in the mepolizumab clinical trial programme. Of the 19 distinct omalizumab RCTs only 5 studies were eligible for end point analysis (Humbert et al., 2005,[58] Chanez et al., 2010,[69] Hanania et al., 2011,[61] Niven et al., 2008[73] and Bousquet et al., 2011[74]). However, only 4 of the 5 studies reported relevant outcome data (Humbert et al., 2005,[58] Hanania et al., 2011[61], Niven et al., 2008[73] and Bousquet et al., 2011[74]). Table 58 tabulates the reasons for NMA study inclusion and exclusion of all 19 omalizumab studies and three mepolizumab RCTs, identified by the systematic literature review including data reported by outcome.

In Table 59 the studies eligible for the NMA population 3 'Full trial' prior to assessment of reported outcomes, for each of the 4 analyses are shown. Table 60 further tabulates the mepolizumab and omalizumab studies eligible for each NMA for population 3 'Full trial' by NMA scenario and outcome. The main submission details only the results for Population 3 based on double blind RCT data and for mepolizumab pooling IV and SC arms. A summary of the three alternative scenarios for population 3 are presented in this main body of text however the detail for these 3 alternative scenarios is not given (see appendix 8.7). Information relating to NMA populations 1'overlap' and 2 'extended overlap' are provided in appendix 8.7.

Appendix 8.7 provides a comparative summary of the included omalizumab and mepolizumab studies (patient population, trial design, end points etc) reporting relevant outcomes which are also discussed in the summary section of the NMA section 4.10.2. The quality assessment of each of these studies is also provided in appendix 8.7 and section 4.6.1. The final feasible efficacy end points based on availability and consistency of the information reported were:

- Clinically significant exacerbations - defined in accordance with the primary endpoint in MENSA and DREAM: an asthma worsening requiring treatment with systemic corticosteroids and/or hospitalisation and/or emergency room treatment.
- Exacerbations requiring hospital admissions
- Change from baseline in predicted FEV_1.

Table 58 Assessment of Systematic Literature Review-retrieved studies for NMA inclusion

Yes = pass NMA inclusion criterion; No = fail NMA inclusion criterion														
MEPO studies retrieved by SLR	**Outcome of Eligibility Assessment: NMA Inclusion**			**Details of Eligibility Assessment per NMA Inclusion Criteria: MEPO studies**										
				Population / Intervention						***Comparator***	***Study design***			***Outcomes***
	MEPO 100mg SC	**+ open-label studies**	**+ MEPO 75mg IV data**	**MEPO-eligible† patients treated with:**		**OMA-eligible† † patients**	**Patients aged ≥ 12 years**	**Current Tx of ≥1000µg BDP-equiv. ICS/day + ≥1 controller**	**Exac. history (≥ 1 in previous year)†††**	**Placebo plus SoC, or SoC alone**	**RCT**	**Stable dosing regimen**	**Double-blind**	**≥ 1 NMA-relevant endpoint**
				100 mg SC	**75 mg IV**									
GSK data on file, MEA115588 – MENSA study' – MEPO 100 mg SC and MEPO 75mg IV vs. PLA Publication: Ortega 2014	**YES**	**YES**	**YES**	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
GSK data on file, MEA112997 - DREAM study - MEPO 75 mg IV vs. PLA	**NO**	**NO**	**YES**	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1° publication: Pavord 2012	NO	NO	NO	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nair 2009	NO	NO	NO	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Haldar 2009	NO	NO	NO	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bel 2014 - MEA115575 – 'SIRIUS'	**NO**	**NO**	**NO**	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No

OMA studies retrieved by SLR	**Outcome of Eligibility Assessment: NMA Inclusion**		**Details of Eligibility Assessment per NMA Inclusion Criteria: OMA studies**								
			Population / Intervention				***Comparator***	***Study design***			***Outcomes***
	DB only	**+ open-label studies**	**OMA-eligible†† patients**	**Patients aged ≥ 12 years**	**Current Tx of ≥1000µg BDP-equiv. ICS/day**	**Exac. history (≥ 1 in previous year)†††**	**Placebo plus SoC, or SoC alone**	**RCT**	**Stable dosing regimen**	**Double-blind**	**≥ 1 NMA-relevant endpoint**
'INNOVATE' Humbert 2005	**YES**	**YES**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sthoeger 2007	YES	YES	*Secondary publication; assessment identical to main publication*								
Humbert 2008	YES	YES	*Secondary publication; assessment identical to main publication*								

Chanez 2010	**YES**	**YES**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
'EXTRA' Hanania 2011	**YES**	**YES**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hanania 2013	YES	YES	*Secondary publication; assessment identical to main publication*								
Bousquet 2011	**NO**	**YES**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Siergiejko 2011	NO	YES	*Secondary publication; assessment identical to main publication*								
Holgate 2004	NO	NO	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Ayres 2004	NO	NO	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Niven 2008	**NO**	**YES**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Bardelas 2012	**NO**	**NO**	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Busse 2001	**NO**	**NO**	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Finn 2003	NO	NO	*Secondary publication; assessment identical to main publication*								
Lanier 2003	NO	NO	*Secondary publication; assessment identical to main publication*								
Garcia 2013	**NO**	**NO**	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hoshino 2012	**NO**	**NO**	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Massanari 2010	**NO**	**NO**	Yes	Yes	No	No	Yes	Yes	No	Yes	No
Ohta 2009	**NO**	**NO**	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Rubin 2012	**NO**	**NO**	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Solèr 2001	**NO**	**NO**	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Buhl 2002	NO	NO	*Secondary publication; assessment identical to main publication*								
Buhl 2002	NO	NO	*Secondary publication; assessment identical to main publication*								
Bousquet 2004	NO	NO	*Secondary publication; assessment identical to main publication*								
Zakaria 2013	**NO**	**NO**	*Secondary publication; assessment identical to main publications**								
Milgrom 1999	**NO**	**NO**	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes
eXplore NCT00670930	**NO**	**NO**	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No
Busse 2013	**NO**	**NO**	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Vignola 2004	**NO**	**NO**	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

† MEPO eligibility is based on the expected licence

†† OMA eligibility is based on patients fulfilling the criteria for ≥1 OMA licence, the full definition is given in the 'Population feasibility' section below. For MEPO studies, this criterion is necessary only for the NMA Pop #1 'Overlap' and NMA Pop #2 'Expanded overlap' populations.

††† This is the less restrictive exacerbation history criteria applied for both the NMA Pop #2 'Expanded overlap' and NMA Pop #3 'Full trial' populations. To identify studies included in the NMA Pop #1 'Overlap' population a stricter criterion of ≥ 2 OCS-treated exacerbation or ≥ 1 severe exacerbation resulting in hospitalisation in previous 12 months was applied. This criterion is used to identify 'MEPO eligible' populations at the study level in OMA studies.

* Zakaria 2013 is a pooled analysis of two excluded studies; Busse 2001 and Solèr 2001.

Table 59 Overview of NMAs for Population 3 'Full trial' and corresponding evidence base, before considering data availability for individual NMAs outcomes

ITC Population with rationale	**ITC Scenario: Study Design and Interventions/ Comparators**	**ITC Evidence Base**			
		Eligible MEPO RCTs		**Eligible OMA RCTs *before considering ITC outcome availability***	
		Studies	**Total Patients MEPO/PLA/Total**	**Studies**	**Total Patients OMA/PLA/Total**
NMA population 3 'Full trial' An alternative specification that includes the entire MEPO-eligible dataset	RCTs, MEPO 100 mg SC + 75 mg IV, double blind RCTs only	MENSA DREAM	511/328/839	INNOVATE Humbert *et al.* (2005)[58] Chanez *et al.* (2010)[69] Hanania *et al.* (2011)[61]	656/642/1,298
	RCTs, MEPO 100 mg SC IV, double blind RCTs only	MENSA	194/191/385	INNOVATE Humbert *et al.* (2005)[58] Chanez *et al.* (2010)[69] Hanania *et al.* (2011)[61]	656/642/1,298
	MEPO 100mg SC + Open-label studies	MENSA		INNOVATE Humbert *et al.* (2005)[58] Chanez *et al.* (2010)[69] Hanania *et al.* (2011)[61] Niven *et al.* (2008)[73] EXALT Bousquet et al. (2011)[74]	1,043/819/1,862
	MEPO 100 mg SC + 75 mg IV + open label studies	MENSA DREAM	511/328/839	INNOVATE Humbert *et al.* (2005)[58] Chanez *et al.* (2010)[69] Hanania *et al.* (2011)[61] Niven *et al.* (2008)[73] EXALT Bousquet et al. (2011)[74]	1,043/819/1,862

A total of 5 omalizumab RCTs were eligible for at least one specification of the NMA, based on population, intervention/comparator and study design criteria. However, not all studies reported all ITC endpoints; in fact, one omalizumab study did not report any relevant efficacy endpoints, and another did not report any relevant safety endpoints. As a result, the omalizumab evidence base varied by endpoint up to a maximum of 4 omalizumab RCTs.
Omalizumab in EU: Severe persistent allergic asthma; Eligible baseline IgE levels ≥ 30 IU/mL to ≤ 1,500 IU/mL; Weight ≥ 20 kg to <150 kg; Maximum dosage of 600mg SC every 2 weeks.
NMA Inclusion Criteria – Study Design: Parallel-group RCT; Double-blind study; RCT duration ≥ 12 weeks; Where a protocol-driven change in ICS/OCS maintenance dosage is implemented, only those data from periods prior to the change may be included in the ITC; At least one pre-defined and comparable outcome can be extracted or calculated from the available RCT data.
ITC Inclusion Criteria – Interventions/Comparators: Mepolizumab100mg SC + 75mg IV plus SoC; omalizumab doses compatible with local licensed/reimbursed omalizumab prescribing criteria; SoC, or placebo plus SoC.
Abbreviations: ED = Emergency department; ICS = Inhaled corticosteroid; ITC = Indirect treatment comparison; IV = intravenous; MEPO = Mepolizumab; N/A = Not applicable; OCS = Oral corticosteroid; OMA =Omalizumab; RCT = Randomised controlled trial; SC = subcutaneous; SoC = standard of care

Table 60 Mepolizumab and omalizumab RCTs eligible for each ITC specification, by ITC outcomes.

ITC Population with rationale	**ITC Sensitivity Scenarios (Study Design and Interventions-Comparators)**	**ITC Outcome**	**Included MEPO RCTs**				**Included OMA RCTs**						
			# of MEPO RCTs with data	**Total Patients MEPO/ PLA/ Total**	**MEA115588 'MENSA'**	**MEA112997 'DREAM'**	**# of OMA RCTs with data**	**Total Patients OMA/ PLA/ Total**	**'INNOVATE' Humbert *et al.* (2005)**	**Chanez *et al.* (2010)**	**'EXTRA' Hanania *et al.* (2011)**	**Niven *et al.* (2008)**	**Bousquet *et al.* (2011)**
<u>ITC Pop #3 'Full trial'</u> An alternative specification that includes the entire MEPO-eligible dataset	**MEPO 100mg SC + 75mg IV**	Clinically significant exacerbations	2	511/328/839	✓	✓	2	636/631/1,267	✓	NR	✓	N/A	N/A
		Hospitalisations	2		✓	✓	1	209/210/419	✓	NR	NR	N/A	N/A
		Change from baseline in % predicted FEV_1	2		✓	✓	1		✓	NR	NR	N/A	N/A
	MEPO 100mg SC	Clinically significant exacerbations	1	194/191/385	✓	N/A	2	636/631/1,267	✓	NR	✓	N/A	N/A
		Hospitalisations	1		✓	N/A	1	209/210/419	✓	NR	NR	N/A	N/A
		Change from baseline in % predicted FEV_1	1		✓	N/A	1		✓	NR	NR	N/A	N/A
	MEPO 100mg SC + open-label	Clinically significant exacerbations	1		✓	N/A	4	1,023/ 808/1,831	✓	NR	✓	✓	✓
		Hospitalisations	1		✓	N/A	2	481/338/819	✓	NR	NR	NR	✓
		Change from baseline in % predicted FEV_1	Specification/data equivalent to ITC Pop #3 'Full trial' - Base Case - Change from baseline in % predicted FEV_1										
	MEPO 100mg SC + 75mg IV + open-label	Clinically significant exacerbations	2	511/328/839	✓	✓	4	1,023/ 808/1,831	✓	NR	✓	✓	✓
		Hospitalisations	2		✓	✓	2	481/338/819	✓	NR	NR	NR	✓
		Change from baseline in % predicted FEV_1	Specification/data equivalent to ITC Pop #3 'Full trial' - + MEPO 100mg SC+ 75mg IV - Change from baseline in % predicted FEV_1										

ITC Population with rationale	**ITC Sensitivity Scenarios (Study Design and Interventions-Comparators)**	**ITC Outcome**	**Included MEPO RCTs**				**Included OMA RCTs**						
			# of MEPO RCTs with data	**Total Patients MEPO/ PLA/ Total**	**MEA115588 'MENSA'**	**MEA112997 'DREAM'**	**# of OMA RCTs with data**	**Total Patients OMA/ PLA/ Total**	**'INNOVATE' Humbert *et al.* (2005)**	**Chanez *et al.* (2010)**	**'EXTRA' Hanania *et al.* (2011)**	**Niven *et al.* (2008)**	**Bousquet *et al.* (2011)**
Omalizumab in EU: Severe persistent allergic asthma; Eligible baseline IgE levels ≥ 30 IU/mL to ≤ 1,500 IU/mL; Weight ≥ 20 kg to <150 kg; Maximum dosage of 600mg SC every 2 weeks. NMA Inclusion Criteria – Study Design: Parallel-group RCT; Double-blind study; RCT duration ≥ 12 weeks; Where a protocol-driven change in ICS/OCS maintenance dosage is implemented, only those data from periods prior to the change may be included in the ITC; At least one pre-defined and comparable outcome can be extracted or calculated from the available RCT data. NMA Inclusion Criteria – Interventions/Comparators: Mepolizumab 100mg SC+75mg IV plus SoC; omalizumab doses compatible with local licensed/reimbursed omalizumab prescribing criteria; SoC, or placebo plus SoC. **Abbreviations**: ICS = Inhaled corticosteroid; ITC = Indirect treatment comparison; IV = intravenous; MEPO = Mepolizumab; N/A = Not applicable [trial not eligible for inclusion in this specification]; NR = [Outcome] not reported; OCS = Oral corticosteroid; OMA =Omalizumab; RCT = Randomised controlled trial; SC = subcutaneous; SoC = standard of care												

4.10.3 Method of analysis

A Bayesian random-effects meta-analysis with meta-regression and bias adjustment in the presence of heterogeneity was conducted.[139] A constant interaction effect was assumed for all treatments (please refer to appendix 8.7). The analyses were conducted using WinBUGS version 14. The WinBUGS code is provided in the reference pack. Quality checking and forest plots were generated with SAS version 9.3.

4.10.4 Results

Table 61 provides a summary of all the NMA results by population and scenario from the fixed effects model. The following section then describes in detail the base case results for population 3 (IV+SC mepolizumab data) which includes the full mepolizumab dataset and the expanded overlap population (≥ 1 exacerbation in the previous 12 months (treatment with OCS or hospitalisation or ED visit) for omalizumab.

Table 61 Summary results for all endpoints for ITC population 3 'Full trial' [Fixed effects model unless otherwise stated]

ITC Population with rationale	**ITC Outcome**	**Favours MEPO**		**Favours OMA**	
		Mean/Median*[3] Estimate (95% CrI)	Probability MEPO ranked first for treatment effect	Mean/Median[3] Estimate Estimate (95% CrI)	Probability OMA ranked first for treatment effect
ITC Pop #3 'Full trial' Includes the entire MEPO-eligible dataset	**Clinically significant exacerbation rate**				
	Mepolizumab 75mg IV and 100mg SC only (db RCT only)	RR 0.664* (0.513,0.860)	99.9%	X	X
	Mepolizumab 100mg SC only (db RCT only)	RR 0.634* (0.449, 0.892)	99.6%	X	X
	Mepolizumab 100mg SC only + open label *[Random effects model]*	RR 0.771* (0.218,2.946)	73.2%	X	X
	Mepolizumab 75mg IV and 100mg SC only + open label *[Random effects model]*	RR 0.798* (0.414,1.613)	80.6%	X	X
	Hospitalisation rate				
	Mepolizumab 75mg IV and 100mg SC only (db RCT only	RR 0.932* (0.350, 2.490)	55.4%	X	X
	Mepolizumab 100mg SC only (db RCT only)	RR 0.576* (0.155, 2.126)	79.3%	X	X
	Mepolizumab 100mg SC only + open label	RR 0.686* (0.200,2.341)	72.5%	X	X
	Mepolizumab 75mg IV and 100mg SC only + open label	X	X	RR 0.901* (0.378,2.143)	59.3%
	Change from baseline in % predicted FEV_1				
	Mepolizumab 75mg IV and 100mg SC only (db RCT only	Mean Diff. 0.645 (-2.652,3.959)	64.7%	X	X
	Mepolizumab 100mg SC only (db RCT only)	Mean Diff. 0.243 (-3.606, 4.097)	54.8%	X	X
	Mepolizumab 100mg SC only + open label	*As per Mepolizumab 100mg SC only (db RCT only)*			
	Mepolizumab 75mg IV and 100mg SC only + open label	*Mepolizumab 75mg IV and 100mg SC only (db RCT only)*			

[1] Omalizumab in EU: Severe persistent allergic asthma; Eligible baseline IgE levels ≥ 30 IU/mL to ≤ 1,500 IU/mL; Weight ≥ 20 kg to <150 kg; Maximum dosage of 600mg SC every 2 weeks. [2] ITC Inclusion Criteria – Study Design: Parallel-group RCT; Double-blind study; RCT duration ≥ 12 weeks; Where a protocol-driven change in ICS/OCS maintenance dosage is implemented, only those data from periods prior to the change may be included in the ITC; At least one pre-defined and comparable outcome can be extracted or calculated from the available RCT data. ITC Inclusion Criteria – Interventions/Comparators: mepolizumab 100mg SC plus SoC; omalizumab doses compatible with local licensed/reimbursed omalizumab prescribing criteria; SoC, or placebo plus SoC. [3] Median is reported for rate ratios (RR).**Abbreviations**: CrI = Credible interval; ICS = Inhaled corticosteroid; ITC = Indirect treatment comparison;

4.10.4.1 Result 1: Pop #3- 'Full trial' – (includes mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Clinically significant exacerbations

For the NMA of mepolizumab and omalizumab on the outcome 'clinically significant exacerbations' RCTs containing treatment arms of mepolizumab 100mg SC and 75mg IV and omalizumab formed the network for meta-analysis, with placebo being the common reference (Figure 20). Four studies were identified in the connected network. Table 62 presents the data extracted from the 4 ITC eligible studies for this analysis of clinically significant exacerbations.

Figure 20 Network diagram – NMA Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Clinically significant exacerbations

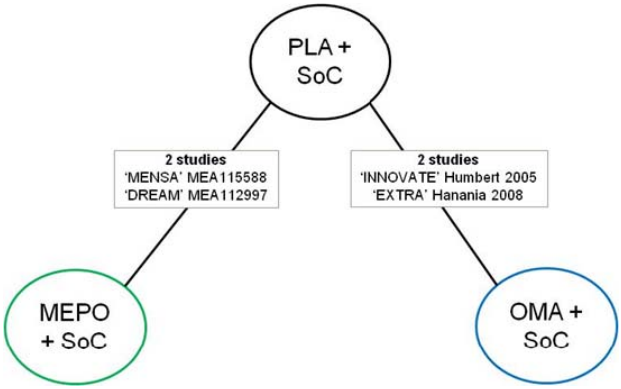


Table 62 Input data – NMA Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Clinically significant exacerbations

Included MEPO data	**Rate Ratio of MEPO vs. PLA**						
	No. of Patients MEPO/PLA/total	**Mean RR**	**Time period (weeks)**	**SE of LogRR**	**SD**	**Lower 95% CI**	**Upper 95% CI**
MENSA (MEPO 100mg SC, MEPO 75mg IV and PLA patients)	385/191/576	0.503	32	0.128	N/A	0.391	0.647
DREAM (MEPO 75mg IV and PLA patients)	126/137/263	0.485	52	0.163	N/A	0.353	0.668
Included OMA data	**Estimated Rate Ratio of OMA vs. PLA**						
	No. of Patients OMA/PLA/Total	**Mean RR**	**Time period (weeks)**	**SE of LogRR**	**SD**	**L 95% CI**	**U 95% CI**
'INNOVATE' Humbert et al. (2005)	209/210/419	0.738	28	0.151*	N/R	0.552	0.998
'EXTRA' Hanania et al. (2011)	427/421/848	0.750	48	0.105*	N/R	0.610	0.920

*LogSE was derived by back-calculation from the logarithm of the rate ratio and 95% CI ([Log(Upper95%CL) - Log(Low95%CL)]/[2*1.96]) because LogSE was not reported in the publication

[1] MEA115588, GSK data on file (study published as Ortega et al., 2014)

[2] MEA112997, GSK data on file (study published as Pavord et al, 2012)

[3] Humbert, M., et al. 2005. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 60; 309-316.

[4] Hanania, N., et al. 2011. Omalizumab in Severe Allergic Asthma Inadequately Controlled With Standard Therapy. *Annals of Internal Medicine*. 154; 573-582.

Abbreviations: CI = Confidence interval; ITC = Indirect treatment comparison; MEPO = Mepolizumab; N/A = Not applicable; N/R = Not reported; OMA =Omalizumab; PLA = Placebo; RCT = Randomised controlled trial; RR = Rate ratio; SC = Subcutaneous Injection; SD = Standard deviation; SE = Standard error

Table 63 provides the results of both fixed and random effects models. Comparing the fit of these models, using the posterior mean of the residual deviance, indicated that the fixed effects model had a slightly better fit to the data (2.033 versus 2.975 respectively). The DICs suggested there was little to choose between these models. The fixed effects model indicated a 33.6% reduction in clinically significant exacerbations in patients treated with mepolizumab compared with omalizumab. The treatment effect of mepolizumab was superior in 99.9% of iterations. A forest plot of the results is shown in Figure 21.

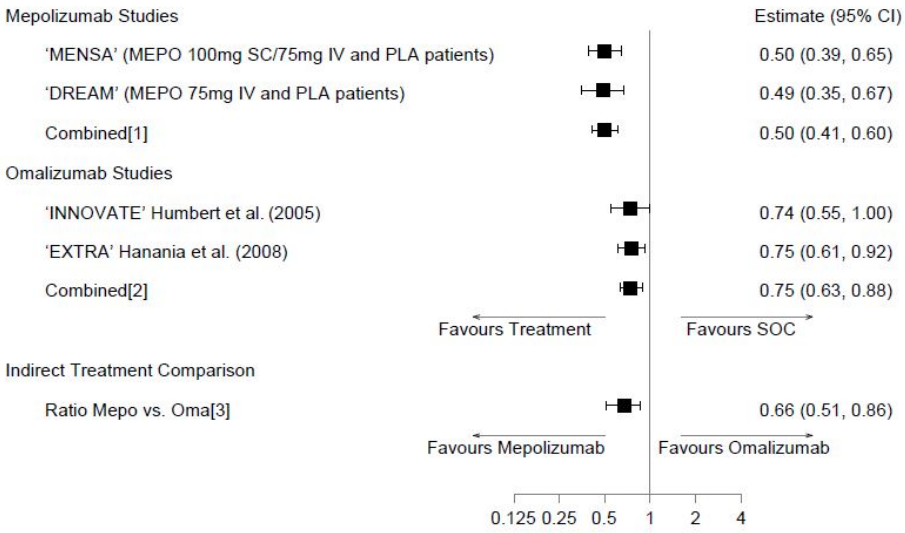
Table 63 Results of fixed-effects and random-effects models - ITC Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Clinically significant exacerbations

	Fixed-effects model Mean/ Median*			Random-effects model Prior of σ: unif(0,2)		
	Mean/ Median*	SD	CrI (2.5%, 97.5%)	Mean/ Median*	SD	CrI (2.5%, 97.5%)
LogRR	-0.409	0.132	-0.668, 0.151	-0.412	0.425	-1.261, 0.404
RR	0.664*	0.089	0.513, 0.860	0.664*	1.059	0.283, 1.498
σ	-	-	-	0.129*	0.323	0.005, 1.291
Totresdev	2.033			2.975		
pD	1.994			2.964		
DIC	-4.650			-2.737		
Probability MEPO is better than OMA	0.999			0.928		
Probability MEPO is best	0.999			0.924		

*Median is reported for RR and σ

Abbreviations: CrI = Credible interval; DIC = Deviance information criterion; ITC = Indirect treatment comparison; MEPO = Mepolizumab; OMA = Omalizumab; pD = Posterior mean deviance; RCT = Randomised controlled trial; RR = Rate ratio; SD = Standard deviation; Totresdev = Total residual deviance

Figure 21 Forest plot based on fixed-effects model - NMA Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Clinically significant exacerbations



[1] I-squared: N/A
[2] I-squared: N/A
[3] Result of a fixed-effects model

Table 64 and Table 65 shows that of the three comparators mepolizumab, omalizumab and placebo, the probability that each treatment was ranked first for treatment effect was 0.999, 0 and 0 respectively.

Table 64 Results for relative effects based on fixed-effects model - NMA Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Clinically significant exacerbations

Intervention		Comparator		
		Mepolizumab	Omalizumab	Placebo
Mepolizumab	Estimate (median) 95% CrI P(better than comparator)		0.664 (0.513, 0.860) >99.9%	0.496 (0.407, 0.603) >99.9 %
Omalizumab	Estimate (median) 95% CrI P(better than comparator)	1.506 (1.163, 1.950) <0.01%		0.746 (0.630, 0.883) >99.9%
Placebo	Estimate (median) 95% CrI P(better than comparator)	2.017 (1.659, 2.458) <0.01%	1.340 (1.132, 1.586) <0.01%	

Table 65 Ranking of probability that each treatment is the best, based on fixed-effects model - - ITC Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Clinically significant exacerbations

Ranking	Treatment	Probability of being the best treatment
1	Mepolizumab	0.999
2	Omalizumab	0.001
3	Placebo	0.0

4.10.4.2 Result 2 NMA Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Exacerbations requiring hospitalisation

For the indirect comparison of mepolizumab and omalizumab on the outcome 'exacerbations requiring hospitalisation' RCTs containing treatment arms of mepolizumab 100mg SC and 75mg IV and omalizumab formed the network for meta-analysis, with placebo being the common reference (Figure 22). Three studies were identified in the connected network.

Table 66 presents the data extracted from the 3 ITC eligible studies for this analysis of exacerbations requiring hospitalisation.

Figure 22 Network diagram –ITC Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Exacerbations requiring hospitalisation

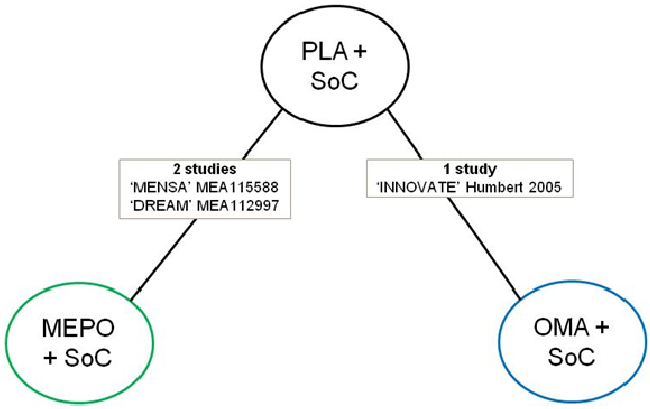


Table 66 Input data – NMA Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Exacerbations requiring hospitalisation

Included MEPO data	Rate Ratio of MEPO vs. PLA						
	No. of Patients MEPO/PLA/total	Mean RR	Time period (weeks)	SE of LogRR	SD	Lower 95% CI	Upper 95% CI
MENSA (MEPO 100mg SC, MEPO 75mg IV and PLA patients)	385/191/576	0.442	32	0.428	N/A	0.191	1.022
DREAM[2] (MEPO 75mg IV and PLA patients)	126/137/263	0.589	52	0.460	N/A	0.239	1.451

Included OMA data	Estimated Rate Ratio of OMA vs. PLA						
	No. of Patients OMA/PLA/Total	Mean RR	Time period (weeks)	SE of LogRR	SD	L 95% CI	U 95% CI
'INNOVATE' Humbert et al. (2005)[3]	209/210/419	0.540	28	0.393*	N/R	0.250	1.166

*LogSE was derived by back-calculation from the logarithm of the rate ratio and 95% CI ([Log(Upper95%CL) - Log(Low95%CL)]/[2*1.96]) because LogSE was not reported in the publication

[1] MEA115588, GSK data on file (study published as Ortega et al., 2014)

[2] MEA112997, GSK data on file (study published as Pavord et al, 2012)

[3] Humbert, M., et al. 2005. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 60; 309-316.

Abbreviations: CI = Confidence interval; ITC = Indirect treatment comparison; MEPO = Mepolizumab; N/A = Not applicable; N/R = Not reported; OMA =Omalizumab; PLA = Placebo; RCT = Randomised controlled trial; RR = Rate ratio; SC = Subcutaneous Injection; SD = Standard deviation; SE = Standard error

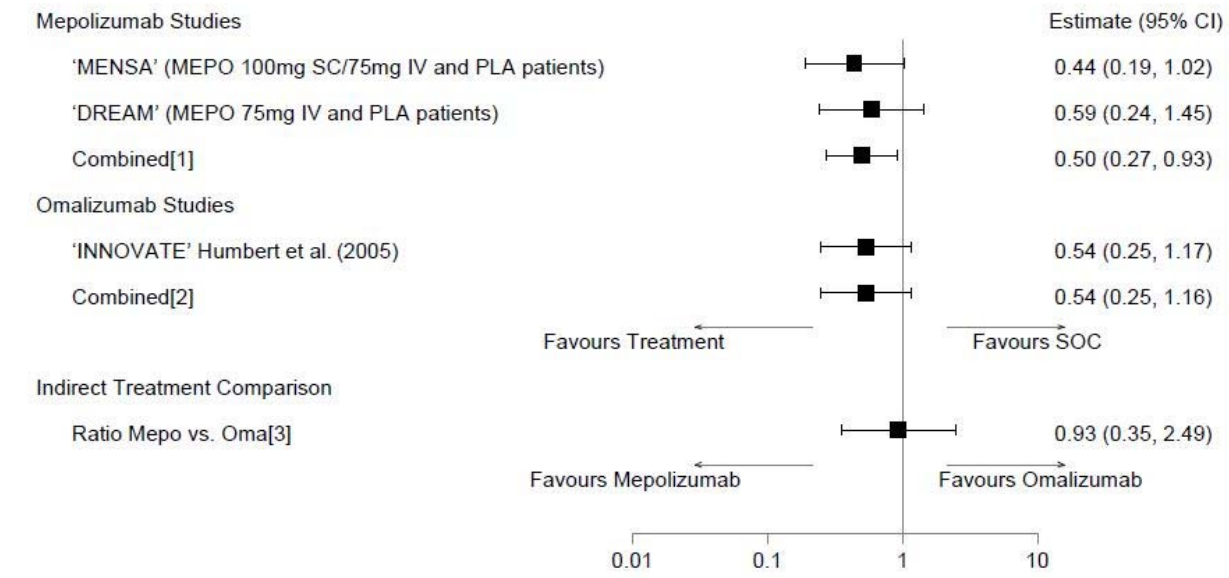
Table 63 provides the results of both fixed and random effects models. Comparing the fit of these models, using the posterior mean of the residual deviance, indicated that the fixed effects model had a slightly better fit to the data (2.203 versus 2.364 respectively). The DICs suggested there was little to choose between these models. The fixed effects model indicate a 6.8% reduction in clinically significant exacerbations requiring hospitalisation in patients treated with mepolizumab compared with omalizumab. The treatment effect favoured mepolizumab 55.5% of iterations however the 95% Credible Interval crossed one. A forest plot of the results is shown in Figure 23.

Table 67 Results of fixed-effects and random-effects models - NMA Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Exacerbations requiring hospitalisation

	Fixed-effects model Mean/ Median*			Random-effects model Prior of σ: unif(0,0.5)		
	Mean/ Median*	SD	CrI (2.5%, 97.5%)	Mean/ Median*	SD	CrI (2.5%, 97.5%)
LogRR	-0.071	0.501	-1.049, 0.912	-0.063	0.606	-1.257, 1.118
RR	0.932*	0.563	0.350, 2.490	0.937*	0.758	0.285, 3.059
σ	-	-	-	0.228*	0.143	0.011, 0.484
Totresdev	2.203			2.364		
pD	1.994			2.239		
DIC	4.593			4.998		
Probability MEPO is better than OMA	0.555			0.542		
Probability MEPO is best	0.554			0.540		

*Median is reported for RR and σ
Abbreviations: CrI = Credible interval; DIC = Deviance information criterion; ITC = Indirect treatment comparison; MEPO = Mepolizumab; OMA = Omalizumab; pD = Posterior mean deviance; RCT = Randomised controlled trial; RR = Rate ratio; SD = Standard deviation; Totresdev = Total residual deviance

Figure 23 Forest plot based on fixed-effects model - NMA Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Exacerbations requiring hospitalisation



[1] I-squared: N/A
[2] I-squared: N/A
[3] Result of a fixed-effects model

Table 67 and Table 68 shows that of the three comparators mepolizumab, omalizumab and placebo, the probability that each treatment was ranked first for treatment effect was 0.554, 0.445 and 0 respectively.

Table 68 Results for relative effects based on fixed-effects model - ITC Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Exacerbations requiring hospitalisation

Intervention		Comparator		
		Mepolizumab	Omalizumab	Placebo
Mepolizumab	Estimate (median) 95% CrI P(better than comparator)		0.932 (0.350, 2.490) 55.5%	0.504 (0.273, 0.928) 98.6%
Omalizumab	Estimate (median) 95% CrI P(better than comparator)	1.073 (0.402, 2.854) 44.5%		0.542 (0.250, 1.164) 94.2%
Placebo	Estimate (median) 95% CrI P(better than comparator)	1.983 (1.078, 3.665) 1.4%	1.847 (0.859, 3.998) 5.8%	

Table 69 Ranking of probability that each treatment is the best, based on fixed-effects model - NMA Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Exacerbations requiring hospitalisation

Ranking	Treatment	Probability of being the best treatment
1	Mepolizumab	0.554
2	Omalizumab	0.445
3	Placebo	0.001

4.10.4.3 Result 3 - NMA Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Change from baseline in % predicted FEV_1

For the indirect comparison of mepolizumab and omalizumab on the outcome 'change from baseline in % predicted FEV_1' RCTs containing treatment arms of mepolizumab 100mg SC and 75mg IV and omalizumab formed the network for meta-analysis, with placebo being the common reference (Figure 20). Three studies were identified in the connected network. Table 70 presents the data extracted from the 3 ITC eligible studies for this analysis of change from baseline in % predicted FEV_1.

Figure 24 Network diagram – NMA Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Change from baseline in % predicted FEV_1

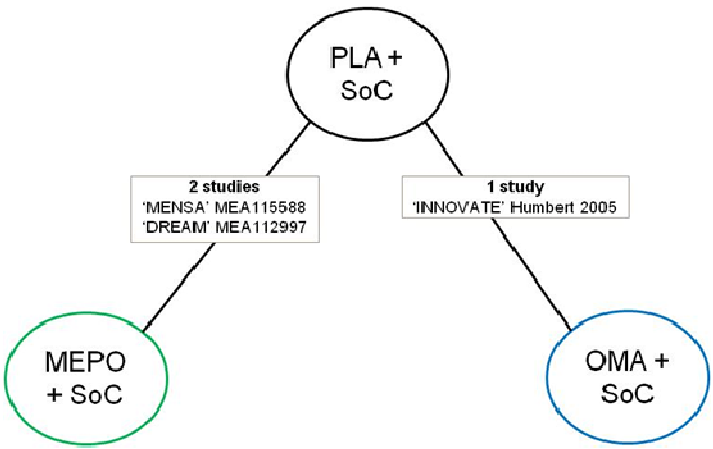


Table 70 Input data – NMA Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Change from baseline in % predicted FEV_1

Included MEPO data	Difference in mean change from baseline in % predicted FEV_1 of MEPO vs. PLA					
	No. of Patients MEPO/PLA/total	Mean diff.	Time period (weeks)	SE	Lower 95% CI	Upper 95% CI
'MENSA' MEA115588[1] (MEPO 100mg SC, MEPO 75mg IV and PLA patients)	385/191/576	3.302	32	1.223	0.630	5.433
'DREAM' MEA112997[2] (MEPO 75mg IV and PLA patients)	191/191/382	4.257	52	1.677	0.961	7.552
Included OMA data	**Difference in mean change from baseline in % predicted FEV_1 of OMA vs. PLA**					
	No. of Patients OMA/PLA/Total	**Mean diff.**	**Time period (weeks)**	**SE**	**Lower 95% CI**	**Upper 95% CI**
'INNOVATE' Humbert et al. (2005)[3]	209/210/419	2.80	28	1.380	0.100	5.500

[1] MEA115588, GSK data on file (study published as Ortega et al., 2014)

[2] MEA112997, GSK data on file (study published as Pavord et al, 2012)

[3] Humbert, M., et al. 2005. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 60; 309-316.

Abbreviations: CI = Confidence interval; ITC = Indirect treatment comparison; MEPO = Mepolizumab; N/A = Not applicable; N/R = Not reported; OMA =Omalizumab; PLA = Placebo; RCT = Randomised controlled trial; RR = Rate ratio; SC = Subcutaneous Injection; SD = Standard deviation; SE = Standard error

Table 71 provides the results of both fixed and random effects models. Comparing the fit of these models, using the posterior mean of the residual deviance, indicated that the fixed effects model had a slightly better fit to the data (2.343 versus 2.373 respectively). The DICs suggested there was little to choose between these models. The fixed effects model indicate a 0.645% improvement in the mean change from baseline in % predicted FEV_1 in patients treated with mepolizumab compared with omalizumab. The treatment effect favoured mepolizumab in 64.7% of iterations, however the 95% Credible interval did cross 1. A forest plot of the results is shown in Figure 25.

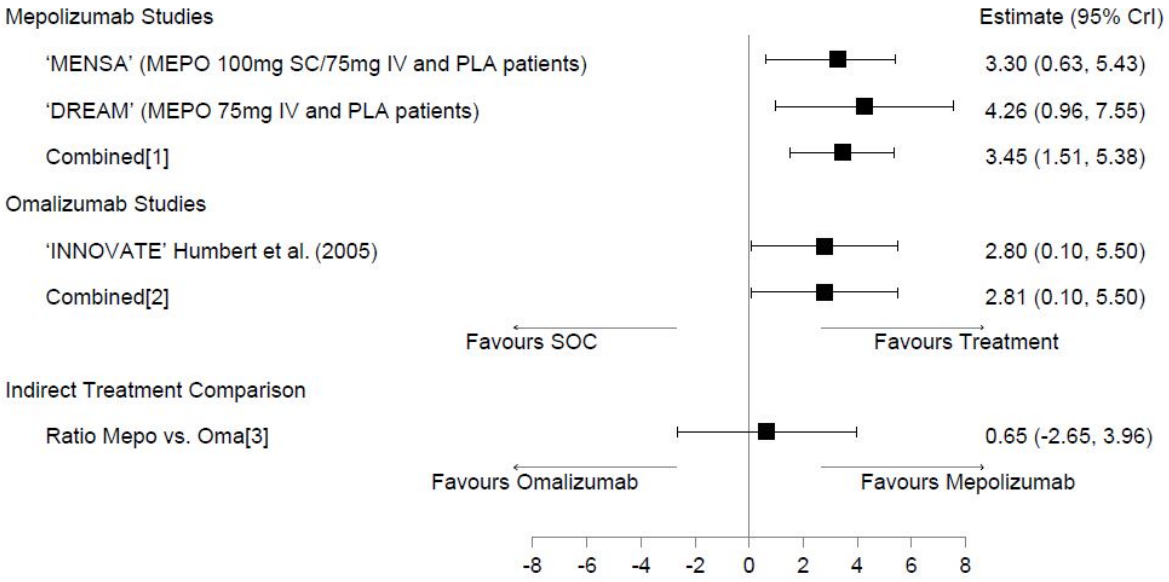
Table 71 Results of fixed-effects and random-effects models – NMA Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Change from baseline in % predicted FEV_1

	Fixed-effects model			Random-effects model Prior of σ: unif(0,1)		
	Mean/ Median*	SD	CrI (2.5%, 97.5%)	Mean/ Median*	SD	CrI (2.5%, 97.5%)
Mean Diff.	0.645	1.691	-2.652, 3.959	0.653	1.816	-2.882, 4.234
σ	-	-	-	0.488*	0.288	0.024, 0.974
Totresdev	2.343			2.373		
pD	1.994			2.101		

DIC	11.931	12.068
Probability MEPO is better than OMA	0.647	0.639
Probability MEPO is best	0.647	0.639

*Median is reported for
Abbreviations: CrI = Credible interval; DIC = Deviance information criterion; ITC = Indirect treatment comparison; MEPO = Mepolizumab; OMA = Omalizumab; pD = Posterior mean deviance; RCT = Randomised controlled trial; RR = Rate ratio; SD = Standard deviation; Totresdev = Total residual deviance

Figure 25 Forest plot based on fixed-effects model – NMA Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Change from baseline in % predicted FEV1



[1] I-squared: N/A
[2] I-squared: N/A
[3] Result of a fixed-effects model

Table 64 and Table 65 shows that of the three comparators mepolizumab, omalizumab and placebo, the probability that each treatment was ranked first for treatment effect was 0.647, 0.353 and 0 respectively.

Table 72 Results for relative effects based on fixed-effects model – ITC Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Change from baseline in % predicted FEV_1

Intervention		**Comparator**		
		Mepolizumab	**Omalizumab**	**Placebo**
Mepolizumab	Estimate (mean) 95% CrI P(better than comparator)		0.645 (-2.652, 3.959) 64.7%	3.449 (1.512, 5.38) >99.9%
Omalizumab	Estimate (mean) 95% CrI P(better than comparator)	-0.645 (-3.959, 2.652) 35.3%		2.805 (0.101, 5.499) 97.9%
Placebo	Estimate (mean) 95% CrI	-3.449 (-5.38, -1.512)	-2.805 (-5.499, -0.100)	

	P(better than comparator)	<0.01%	2.1%	

Table 73 Ranking of probability that each treatment is the best, based on fixed-effects model – ITC Pop #3- 'Full trial' – (Mepolizumab 100mg SC and 75mg IV / Double-blind RCTs only) – Change from baseline in % predicted FEV_1

Ranking	Treatment	Probability of being the best treatment
1	Mepolizumab	0.647
2	Omalizumab	0.353
3	Placebo	0.0

4.10.5 Additional analyses

Results for population #3 (mepolizumab 100mg SC only, adding in non-RCT data and combining IV and SC and non-RCT data) and for populations # 1 and 2 for all scenarios are provided in appendix 8.7.

4.10.6 Discussion

Whilst the NMA provides the first rigorous and comprehensive attempt to compare the effectiveness of mepolizumab and omalizumab the results must be interpreted with caution. In the absence of IPD for the omalizumab data, it would only be possible to obtain estimates of the 'overlap' population from the mepolizumab data. Therefore we have chosen to present NMA analyses of mepolizumab versus omalizumab for the 'Full trial' populations of both treatments. Inclusion of the entirety of the evidence in this population is more balanced for both products i.e. to include patients from both mepolizumab and omalizumab trials that may not be eligible the alternative treatment. For completeness all populations and their results are provided in appendix 8.7. Several important efficacy outcomes which are available for both datasets were analysed as robustly as possible in this ITC and the results represent the best currently available comparative information to support decision makers.

The ITC has demonstrated that mepolizumab is associated with a reduction in clinically significant exacerbations versus omalizumab across the NMA populations. The median estimated rate ratio was 0.664 (95% CrI 0.513, 0.860) for NMA population #3 (SC+IV data for mepolizumab). The analysis of the hospitalisation rate was consistent with the exacerbation analysis. The median estimated rate ratio was 0.932 (95% CrI 0.350, 2.490) for NMA population #3. The analysis of the change from baseline in predicted FEV_1 indicated that mepolizumab and omalizumab are broadly comparable. The point estimate was 0.645 (95% CrI -2.652, 3.959) for NMA population #3. Whilst this section has focused on the results of population 3 which we consider to be most appropriate, if the alternative populations and scenarios are considered, there is consistency in the results observed (reduction in clinically significant exacerbations: 0.761 (95% CrI 0.492,1.176) for NMA population #1 and 0.752 (95% CrI 0.522,1.079) for NMA population #2, hospitalisation rate: 1.347 (95% CrI 0.338, 5.330) for NMA population #1 and #2 and change from baseline in predicted FEV_1: -0.125 (95% CrI -4.288,4.029) for NMA populations #1and #2). However as the evidence base was expanded the results trended to favouring mepolizumab further.

With respect to the analyses shared in this submission (population #3 'Full trial'), evidence is drawn from two RCTs for mepolizumab and two RCTs for omalizumab. At most, the maximum number of patients included in any one analysis does not exceed 2,106 patients. All included studies were randomised, parallel group, placebo controlled studies, all multi-centre although Hanania et al[61] was confined to US and Canada. All studies differed in trial length; DREAM was 52 weeks, MENSA 32 weeks, Humbert et al 28 weeks and Hanania et al 48 weeks. The overall short duration of the included RCTs could limit the interpretation of the findings in terms of extrapolation or projection in time of the potential therapy related harms and benefits. However this is a limitation of the evidence base rather than the NMA conduct itself.

Reviewing the included RCTs shows that patients recruited to the omalizumab trials were marginally younger (mean age ≤45.3 years)[58,61] than those recruited to MENSA and DREAM (mean age approximately 50 years). There was a slightly lower proportion of male patients recruited to the omalizumab trials (approximately one third) compared to MENSA and DREAM (<40% male). Omalizumab trial patients had a higher mean BMI (approximately 31) compared to MENSA and DREAM patients (approximately 28). The key difference in baseline characteristics was that MENSA and DREAM recruited more severe asthma patients as shown by the mean baseline exacerbation frequency of >3 compared with <3 in the omalizumab studies. The quality assessment identified few concerns in the quality of study design and conduct however the method of randomisation was not made clear in Humbert et al and Hanania et al.

All patients recruited into the ITC were at least at Step 4 of the BTS/SIGN treatment algorithm, i.e. on high-dose ICS and additional controller(s). The key difference between the included mepolizumab studies and the included omalizumab studies was that all patients recruited to MENSA and DREAM had to have experienced at least two clinically significant exacerbations in the previous 12 months to the study. Whereas in Humbert et al, patients were included if they experience two exacerbations (requiring OCS) or one severe exacerbation (FEV_1/PEV<60% of personal best requiring OCS) and in Hanania et al patients were required to have experienced at least 1 exacerbation in the previous 12 months defined as an increase in asthma symptoms requiring systemic OCS. A higher treatment effect would be expected in a more severe asthma population. This would have the potential effect of biasing the overall comparative treatment effect towards mepolizumab over omalizumab. However it is important to note that in this NMA, the results for population 2 did not differ substantially from population 1, indicating a low impact of relaxing the exacerbation history requirement for omalizumab RCTs.

Although heterogeneity was anticipated and examined, it was not ultimately possible to conduct meta-regression to adjust for bias for study level co-variates, due to the very small number of studies meeting the NMA inclusion criteria. Overall the studies included in the NMA were deemed sufficiently similar to conduct the comparisons and we believe the consistency assumption is reasonable in this type of data. The models appeared to fit the data well, no loops were found to be inconsistent and model parsimony was always higher for the consistency model; this provided support for our assumption of consistency. However the power of these tests and approaches to detect inconsistency are low, particularly for networks with small

number of included studies. Worthy of note is that the NMAs conducted are predicated on a systematic literature review and so therefore mepolizumab had potential to include unpublished data whereas this was not true for omalizumab.

Despite the consistency of the results across the NMAs, which attempt to estimate the overlap population (appendix 8.7), none of the populations reflect for omalizumab, the NICE recommended population or for mepolizumab, the GSK proposed population for which guidance is sought due to data availability limitations. Both of these populations represent more severe populations than those compared in the NMAs presented.

Further the NMAs conducted are not able to consider the possible resultant treatment effect of omalizumab by eosinophil threshold. In a recent publication, Hanania et al (2013)[62], a post-hoc analysis of the EXTRA study showed that patients with a higher level of eosinophils at baseline (≥260 cells/µl, the median baseline in EXTRA)) experienced a greater reduction in clinically significant exacerbations (32% [95% CI 11-48; p=0.005]) compared to those with a lower level of eosinophils at baseline (<260 cells/µl) (9% [95% CI -24-34 p=0.054]). The exacerbation rate ratio in the baseline ≥260 cells/µL subgroup was approximately 0.68 (estimated from Hanania *et al.,* 2013 Figure 2), compared to the ITT population rate ratio of 0.75 (95% CI 0.61, 0.92) (Hanania *et al.,* 2011)[61]. This result suggests that in those patients with a higher eosinophil threshold at baseline the reduction in clinically significant exacerbations may be greater for omalizumab than that seen and included in this NMA. Not all EXTRA patients would be eligible for mepolizumab, since milder patients were included with ≥1 exacerbation in the previous 12 months to screening, however there is still some evidence to suggest that the current NMA estimates may favour mepolizumab to a degree.

Whilst the absence of IPD omalizumab data means the treatment effect by the eosinophil level required for mepolizumab eligibility cannot be estimated precisely it is unlikely that the impact would be sufficient to change the overall conclusions. The exacerbation rate ratio in MENSA using a baseline threshold of 260 cells/µL (consistent with the EXTRA post hoc analysis) is not available however it has been calculated for the ≥300 cells/ µL subgroup. In the full MENSA population, the relevant value for a ≥260 cells/ µL subgroup would lie somewhere between the ITT rate ratio of 0.47 (95% CI: 0.35, 0.64) for mepolizumab 100mg SC and the ≥300 cells/ µL subgroup rate ratio of 0.36 (95% CI: 0.24, 0.54) for mepolizumab 100mg SC. Therefore, it appears unlikely that a revision of the omalizumab efficacy estimates, if of a magnitude similar to that seen in the EXTRA subgroup analysis, would be large enough to change the conclusions of the NMA on this endpoint.

In conclusion, mepolizumab showed a reduction in clinically significant exacerbations significantly in favour of mepolizumab. In regards to hospitalisation and FEV_1 mepolizumab was broadly comparable to omalizumab. However, this conclusion needs to be interpreted with caution due to the limitations of the available evidence for omalizumab. In addition whilst it is not possible to provide evidence of the relative effectiveness of mepolizumab in the proposed GSK population compared to the NICE recommended omalizumab population due to lack of IPD for omalizumab, given the results in the ITT population it is a reasonable assumption that in the overlap population mepolizumab would be at least as effective as omalizumab.

4.11 Non-randomised and non-controlled evidence

4.11.1 List of relevant non-randomised and non-controlled evidence

Table 74 List of relevant non-randomised and non-controlled evidence

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
MEA114092 (PK/PD Study).	IV Mepolizumab 75mg SC Mepolizumab 12.5mg, 125mg and 250mg	Severe Asthma patients on high dose ICS with documented evidence of elevated blood eosinophil levels (>300 cells/µl) within 12 months of screening and evidence of elevated blood eosinophil levels >300 cells/µL at screening.	PK/PD Study was an open-label clinical pharmacology study to evaluate the PK/PD relationship following mepolizumab IV and SC in subjects with asthma and elevated blood eosinophils.	NCT01366521 https://clinicaltrials.gov/ct2/show/NCT01366521?term=Mepolizumab&rank=13	Dose ranging study[117]
MEA115661 (COSMOS)	SC Mepolizumab 100mg	MENSA or SIRIUS study participants, who completed the double-blind investigational product treatment,	Multi-centre, Open-label, Long-term Safety Study of Mepolizumab in Asthmatic Subjects Who Participated in the MENSA or SIRIUS trials	NCT01842607 https://www.clinicaltrials.gov/ct2/show/NCT01842607?term=mepolizumab&rank=4	Additional safety and efficacy data
MEA115666 (COLUMBA)	SC Mepolizumab 100mg	DREAM participants, who completed the double-blind investigational product treatment.	Multi-centre, open-label, long-term safety study of Mepolizumab in asthmatic subjects who participated in the DREAM trial.	NCT01691859 https://www.clinicaltrials.gov/ct2/show/NCT01691859?term=mepolizumab&rank=12	Additional safety and efficacy data

This section will focus on the open-label extension (OLE) studies of COSMOS and COLUMBA which support the long term safety and efficacy of mepolizumab. The COLUMBA study is still ongoing; however an interim analysis was conducted with data-cut off in February 2014. Therefore, only interim results data for COLUMBA will be presented. The COSMOS study has now concluded and therefore interim and final results data will be discussed. The methods of the studies are shown below Table 75.

The PK/PD study was considered less relevant. However, the publication and CSR have both been provided with the submission.

4.11.2 Methodology of non-RCTs

Table 75 Methodology of non-RCTs (COSMOS and COLUMBA)

Trial number (acronym)	COSMOS	COLUMBA
Trial design	Multicentre, open-label extension, long-term safety study	Multi-centre, open-label extension, long term safety study
Eligibility criteria for participants	● Subjects who had completed double-blind study drug treatment during MENSA or SIRIUS and were treated with controller medication.	● Subjects must have received at least 2 doses of double-blind study drug during the DREAM study. ● If subject received mepolizumab, they must have had a positive risk:

	● Subjects expected to continue controller therapy for duration of study.	benefit ratio in the opinion of the investigator. ● Subject's asthma was being treated with a controller medication, and subject had been on controller medication for the past 12 weeks. ● Subjects expected to continue controller therapy for duration of treatment.
Settings and locations where the data were collected	139 centres across 19 countries, including 20 centres in the USA, 18 in Japan, 12 in Germany, 11 in Canada and France, 10 in Korea, 8 in Italy, 7 in Argentina and the UK, 5 in the Czech Republic and Spain, 4 in Australia, Belgium, Russia and Ukraine, 3 in Chile, and 2 in Mexico, the Netherlands and Poland.	65 centres across 13 countries, including 11 centres in the USA, 8 in Germany, 7 in Russia, 5 in Australia, 4 in Romania, 5 in Ukraine and the UK, 4 in Argentina, Canada, Chile and France, and 2 in Korea and Poland.
Treatment	For patients entering COSMOS who had been on active treatment, there was no interruption of treatment with mepolizumab, while for patients previously receiving placebo, open-label treatment with SC mepolizumab 100mg was initiated at 4-weekly intervals.	This study examines the effects of mepolizumab following cessation and re-start of treatment. Patients will receive treatment for up to 3.5 years. This study is currently ongoing and patients are receiving SC mepolizumab 100mg at 4-weekly intervals.
Primary outcomes	●The frequency of AEs, including both systemic and local site reactions.	● The frequency of AEs, including both systemic and local site reactions.
Secondary/tertiary outcomes	● Frequency of positive anti-mepolizumab binding antibodies and neutralising antibodies. ● Annualised rate of exacerbations. ● Asthma Control Questionnaire (ACQ-5) score. ● FEV_1 measured by clinic spirometry. ● Number of withdrawals due to lack of efficacy. ● Number of withdrawals due to AEs. ● Number of hospitalisations due to AEs including asthma exacerbations. ● Frequency of both systemic (i.e., allergic/immunoglobulin-E (IgE) and local site reactions.	● Frequency of positive anti-mepolizumab binding antibodies and neutralising antibodies. ● Annualised rate of exacerbations. ● Asthma Control Questionnaire (ACQ-5) score. ●FEV_1. ●Number of withdrawals due to lack of efficacy. ● Number of withdrawals due to AEs ● Number of Hospitalisations due to AEs including asthma exacerbations. ● Frequency of both systemic (i.e., allergic/IgE-mediated and non-allergic) and local site reactions.

4.11.3 Statistical analysis of the non-randomised and non-controlled evidence

Statistical Analyses for COSMOS and COLUMBA

Sample size considerations - There was no sample size calculation for either study. The sample size was determined by the number of available subjects who

were randomised into the previous studies (MENSA and SIRIUS for COSMOS, and DREAM for COLUMBA), and were eligible for the current study based on inclusion and exclusion criteria.

Interim analyses - The protocol for both studies specified that interim analysis was performed as needed in order to provide open-label safety data to inform the risk-benefit assessment of mepolizumab in severe asthma. For this report, an interim analysis was performed to support the initial regulatory filing of mepolizumab. The data cut off for this analysis was 28th February 2014 for both studies.

Analysis populations - The All Subjects Enrolled (ASE) Population consisted of all subjects for whom a record exists on the study database. This population was used for listing AEs and summarising reasons for screen failures. The 'As Treated' (AT) Population consisted of all subjects who received at least one dose of mepolizumab. This population was the primary population for all summaries of efficacy and safety measures.

Model covariates - A covariate for region was included in all model-based analyses. Terms for baseline disease severity (as % predicted pre-bronchodilator FEV_1 from the baseline measurement of MENSA or SIRIUS for COSMOS and DREAM for COLUMBA), exacerbations in the year prior to the start of the previous study and time on-treatment was also included when estimating the annualised rate of exacerbations. If there were insufficient subjects in each region or exacerbations category for the statistical procedures to converge satisfactory, further combining of these covariates was considered.

Study Population Analyses - Subject disposition, including reason for withdrawal, was summarised for Screen Failures (ASE population) and the AT population. The proportion of subjects in the AT Population who failed each inclusion or exclusion criterion was summarised. The demographics and baseline characteristics were summarised for each study.

Exposure was summarised as number of treatments administered and the number of days on-treatment. Since the study treatment was being administered in the clinic, treatment compliance was not applicable for either study.

4.11.4 Demographics

The demographics for both COSMOS and COLUMBA have been summarised in the tables below.

Table 76 Demographics for COSMOS

Demographic Characteristic	Mepolizumab 100 mg SC		
	Previous Placebo (N=237)	Previous Mepolizumab (N=414)	All Subjects (N=651)
Age, (years) Mean (SD) Median (Min, Max)	 50.4 (13.42) 51.0 (12, 77)	 51.6 (14.13) 55.0 (13, 83)	 51.1 (13.87) 53.0 (12, 83)
Sex, n (%) Female	125 (53) 112 (47)	235 (57) 179 (43)	360 (55) 291 (45)

Male			
Race, n(%)			
White	192 (81)	338 (82)	530 (81)
Asian	38 (16)	61 (15)	99 (15)
African American/African Heritage	2 (<1)	12 (3)	14 (2)
American Indian or Alaskan Native & White	1 (<1)	2 (<1)	3 (<1)
American India or Alaskan Native	1 (<1)	1 (<1)	2 (<1)
Native Hawaiian or Other Pacific Islander	1 (<1)	0	1 (<1)
African American/African Heritage & White	1 (<1)	0	1 (<1)
Asian & White	1 (<1)	0	1 (<1)
Ethnicity, n (%)			
Not Hispanic/Latino	220 (93)	381 (92)	601 (92)
Hispanic/Latino	17 (7)	33 (8)	50 (8)
Body Mass Index, (Kg/m^2)			
Mean (SD)	28.24 (5.679)	27.89 (5.944)	28.02 (5.847)
Median (Min, Max)	27.47 (17.1, 48.5)	26.88 (16.1, 49.7)	27.17 (16.1, 49.7)

Table 77 Demographics for COLUMBA

Demographic	**Mepolizumab 100 mg SC N=347**
Age, (years)	
Mean (SD)	52.2 (10.73)
Median (Min, Max)	53.0 (21, 75)
Sex, n (%)	
Female	224 (65)
Male	123 (35)
Race, n(%)	
White	318 (92)
Asian	18 (5)
African American/African Heritage	8 (2)
American Indian or Alaskan Native	2 (<1)
Asian & Native Hawaiian or Other Pacific Islander	1 (<1)
Ethnicity, n(%)	
Not Hispanic/Latino	306 (88)
Hispanic/Latino	41 (12)
Body Mass Index, (Kg/m^2)	
Mean (SD)	28.62 (6.10)
Median (Min, Max)	27.43 (17.6, 53.1)

A total of 998 patients from the Exacerbation Studies DREAM and MENSA and the OCS Reduction Study SIRIUS have been enrolled in the OLE Studies (Table 74). More than half of patients who participated in DREAM (347/616, 56%) enrolled in COLUMBA. There was ≥12 month treatment break between the two studies. Most patients who completed either MENSA (522/539, 91%) or SIRIUS (126/135, 93%) elected to continue treatment and directly rolled over into COSMOS. All patients received mepolizumab 100 mg SC in the OLE Studies regardless of their treatment assignment in the double-blind parent study. COLUMBA started before COSMOS, thus patients have longer treatment exposure in this study. As of the February 28, 2014 data cut-off date for the interim analysis, 96% of patients were continuing treatment and there were 643 patient years of exposure. The most common reasons for premature withdrawal from the OLE Studies were adverse event and withdrawal of consent (1% each).

Table 78 Patient disposition and exposures for COSMOS and COLUMBA.

	COLUMBA (Interim)	COSMOS (Final)
Enrolled	347	651
Continuing treatment	325 (94)	N/A
Withdrawn	22 (6)	66 (10)
Completed	N/A	585 (90)
Primary reason for withdrawal		
Adverse event	8 (2)	11(2)
Withdrew consent	8 (2)	14 (2)
Lack of efficacy	0	19 (3)
Protocol deviation	2 (<1)	8 (1)
Physician decision	1 (<1)	9 (1)
Lost to follow-up	2 (<1)	3 (<1)
Met protocol stopping criteria	1 (<1)	2 (<1)

4.11.5 Quality assessment of the relevant non-randomised and non-controlled evidence

In COSMOS, a total of 139 centres in 19 countries enrolled and treated subjects, and in COLUMBA there were a total of 65 centres in 13 countries. COSMOS was initiated on the 27th May 2013, and COLUMBA was initiated on the 28th September 2012 with the date cut off for the interim report being 28th February 2014 for both studies. COSMOS was then completed on 13th May 2015.

For both trials, GSK was responsible for the administration, supply of study drugs, monitoring, analyses, and reporting of the study. The study was managed with applicable regulation, GCP and GSK procedures.

A Clinical Endpoint Committee (CEC) at Duke Clinical Research Institute (Durham, NC USA) adjudicated pre-specified cardiovascular (CV) events and all-cause death that occurred during the conduct of this study to make the determination as to whether particular individual events reported by the investigator met the pre-specified event definition contained within the CEC charter. A quality assessment of the relevant non-RCTs is shown below in

Table 79.

Table 79 Quality assessment of Non-RCTs

Study	COSMOS	COLUMBA
What is the study design of this study?	Open-label extension	Open-label extension
Was the study a prospective study or a retrospective study?	Prospective	Prospective
In case of a case-control study, were the groups similar at the outset of the study in terms of prognostic factors?	N/A	N/A
Was the intervention used appropriately?	Yes	Yes
Were the outcome measures in the study reliable?	Yes	Yes
Were the outcome measures in the study valid?	Yes	Yes
Was the statistical analysis conducted appropriately in the study?	Yes	Yes
Was the quality of reporting appropriate in the study?	Yes	Yes
Can the study results be generalised to routine practice?	Yes	Yes

4.11.6 Clinical effectiveness results of the relevant non-randomised and non-controlled evidence

The clinical effectiveness results will be shown for the As Treated (AT) Populations for both COSMOS and COLUMBA studies. From the subjects initiated into study COSMOS, not all had received mepolizumab in the previous studies. Therefore, these subjects received mepolizumab for the first time at the initiation of COSMOS. The results from the interim report, with data cut-off point being the 28th February 2014 will be shown for both studies, as well as the results from COSMOS when the study completed on the 13th May 2015.

4.11.6.1 Exacerbations

Frequency of exacerbations

Table 80 Overview of All Exacerbations (COSMOS and COLUMBA, AT Population)

	COLUMBA (Interim) Mepolizumab 100 mg SC N=347[1]	COSMOS (Final) Mepolizumab 100 mg SC N=651
On-Treatment Exacerbations		
All exacerbations		
Number of subjects, n (%)	151 (44)	311 (48)
Number of events	301	654
Estimated exacerbation rate per annum	0.67	0.93 (0.83, 1.04)
Exacerbations requiring hospitalisation or ED visit		
Number of subjects, n (%)	25 (7)	59 (9)
Number of events	34	95
Exacerbations requiring hospitalisation		
Number of subjects, n (%)	16 (5)	39 (6)
Number of events	16	65
Post-Treatment Exacerbations[2]		
All exacerbations		
Number of subjects, n (%)	5 (1)	49 (8)
Number of events	5	59
Exacerbations requiring hospitalisation or ED visit		
Number of subjects, n (%)	2 (<1)	10 (2)
Number of events	2	10
Exacerbations requiring hospitalisation		
Number of subjects, n (%)	1 (<1)	8 (1)
Number of events	1	8

1. Includes events that occurred from the start of treatment until 28th February 2014 or the date of withdrawal, but no greater than 4 weeks post last dose. 2. Includes events that occurred in withdrawn subjects beyond their date of withdrawal or that occurred over 4 weeks after their last dose.

In COSMOS, more than half the subjects (52%) had no exacerbation during the study, and in COLUMBA 56% also had no exacerbations as shown in Table 81 below.

Table 81 Frequency and Annualised Rate of All Exacerbations (COSMOS and COLUMBA, AT Population)

	COLUMBA (Interim) Number of Subjects (%) Mepolizumab 100mg SC N=347	COSMOS (Final) Number of Subjects (%) Mepolizumab 100mg SC N=651
Number of Exacerbations		
0	196 (56)	340 (52)
1	90 (26)	149 (23)
2	25 (7)	76 (12)
3	15 (4)	46 (7)
4	7 (2)	20 (3)
5	8 (2)	10 (2)
6	2 (≤1)	5 (<1)

7	1 (≤1)	0
8	0	2 (<1)
9	2 (≤1)	0
≥10	1 (≤1)	3 (<1)
Annualised Rate of Exacerbation		
Exacerbation rate/year (95% CI)	0.67 (0.57, 0.79)	0.93 (0.83, 1.04)

In COSMOS, during the open label treatment with all subjects on mepolizumab, the rates of exacerbations per year remained consistently low from the data cut-off point for the interim report to the final report (0.96 at interim and 0.93 at final). The rate of exacerbations per year for subjects who were previously treated with placebo for 32 weeks in MENSA and switched to mepolizumab also decreased over time during the COSMOS study (from 1.94 to 1.04/year). At the end of the study there was still a majority of 52% of subjects who had not experienced a single exacerbation. This data indicates that the effect of mepolizumab on the reduction of exacerbations is durable and stable over time.

In COLUMBA, there was an interim period after DREAM where patients were not receiving treatment. This period of time ranged from 12 to 28 months, with a mean average of 18.1 months. During this time, subjects experienced an annualised average of 1.74 exacerbations. This number was lower than the 3.6 exacerbations in the year prior to DREAM. Following treatment with SC mepolizumab, the annualised rate of exacerbations was reduced to 0.67, a 61% decrease, with 56% of subjects remaining exacerbation-free at the time of the interim cut-off. While the annualised rate of exacerbations is lower than the on-treatment rate seen in DREAM (1.15-1.46), the percent reduction in exacerbations was consistent.

Hospitalisations due to Exacerbations

Table 82 Summary of Hospitalisation due to Exacerbations (COSMOS and COLUMBA, AT Population)

	COLUMBA (Interim)	**COSMOS (Final)**
	Mepolizumab 100mg SC N=347	**Mepolizumab 100mg SC N=651**
On-Treatment	**Number of Subjects (%)**	**Number of Subjects (%)**
Number of Hospitalisations due to Exacerbations		
0	331 (95)	612 (94)
1	16 (5)	29 (4)
2	N/A	4 (<1)
3	N/A	4 (<1)
6	N/A	1 (<1)
10	N/A	1 (<1)

It can be seen above that in both COSMOS and COLUMBA, there were 94% and 95% of subjects who did not experience any hospitalisations during the study. In COSMOS, at the interim stage 96% of subjects did not experience an exacerbation requiring hospitalisations, which remained relatively consistent as the study

continued as the final report showed that the number had decreased only slightly to 94%. COLUMBA showed that the remaining 5% of subjects only experienced one exacerbation that required hospitalisation over 17 months (initiation date 28/09/2012 to data cut-off 28/02/2014).

4.11.6.2 Durability of response

COSMOS – Subjects treated with mepolizumab had a lower rate of exacerbations per year compared to subjects receiving placebo during the 32-week double blind period of the study MENSA (0.91 versus 1.94/year). During open-label treatment of all subjects with mepolizumab in COSMOS, the rates of exacerbations per year remained low in the subjects who were previously treated with mepolizumab (0.92 for Weeks 32 to 52 and 0.92 for Weeks 52 to 84). The rate of exacerbations per year for the subjects who were previously treated with placebo in MENSA and switched to mepolizumab decreased over time during COSMOS from 1.94 to 1.04 per year (Table 83).

Table 83 Overview of Exacerbation rate by Treatment Allocated within MENSA (MENSA and COSMOS, AT Population)

Treatment period	Placebo (N=191)	Mepolizumab 75 IV/100 SC (N=385)
Subjects who completed COSMOS	159	311
Week 0 - Week 32 (Double-blind)		
Number of events	190	174
Exacerbation rate/year	1.94	0.91
Week 32 - Week 52 (Open-label)		
Number of events	66	110
Exacerbation rate/year	1.08	0.92
Week 52 - Week 84 (Open-label)		
Number of events	101	174
Exacerbation rate/year	1.04	0.92
Subjects with at least 52 Weeks data	170	335
Week 0 - Week 32 (Double-blind)		
Number of events	201	205
Exacerbation rate/year	1.92	0.99
Week 32 - Week 52 (Open-label)		
Number of events	72	132
Exacerbation rate/year	1.10	1.03
Subjects with at least 32 Weeks data	180	361
Week 0 - Week 32 (Double-blind)		
Number of events	210	221
Exacerbation rate/year	1.89	0.99

Note: Includes clinically significant exacerbations from MENSA and all exacerbations from COSMOS MEA115661). Note: Exacerbations summarised according to randomised treatment in MENSA. In general, exacerbations displayed in Weeks 0-32 were experienced on randomised treatment in MENSA, exacerbations displayed in Weeks 32-52 to Weeks 52-84 were experienced on mepolizumab treatment in COSMOS. Weeks 32-52 includes 6 exacerbations experienced in MENSA on mepolizumab.

4.11.6.3 Oral corticosteroid use

During open-label treatment of all subjects with mepolizumab in COSMOS, the use of OCS remained low in the subjects who were previously treated with mepolizumab (2.5mg/day for Weeks 44 to 76). The use of OCS for the subjects who were previously treated with placebo for 24 weeks in SIRIUS and switched to

mepolizumab decreased over time during the COSMOS study (from 10.0 to 5.0 mg/day) as shown in Table 84 below.

Table 84 Summary of OCS dose (mg/day) During Each Reporting Period by Treatment Allocated within SIRIUS (SIRIUS and COSMOS, AT Population)

Treatment period	Placebo (N=191)	Mepolizumab 100 SC (N=385)
Subjects who completed COSMOS		
n	58	57
Median dose (mg/day)		
Double-blind period		
Optimised dose (Baseline)	12.3	10.0
Week 0 Visit - Week 4 Visit	12.5	10.0
Week 4 Visit - Week 8 Visit	10.0	9.1
Week 8 Visit - Week 12 Visit	10.0	5.2
Week 12 Visit - Week 16 Visit	9.7	5.1
Week 16 Visit - Week 20 Visit	10.0	5.0
Week 20 Visit - Week 24 Visit	10.0	2.5
Open-label period		
Week 24 Visit - Week 28 Visit	10.0	2.5
Week 28 Visit - Week 32 Visit	7.5	2.5
Week 32 Visit - Week 36 Visit	6.6	2.9
Week 36 Visit - Week 40 Visit	5.5	2.5
Week 40 Visit - Week 44 Visit	5.7	2.5
Week 44 Visit - Week 48 Visit	5.0	2.5
Week 48 Visit - Week 52 Visit	5.0	2.5
Week 52 Visit - Week 56 Visit	5.0	2.9
Week 56 Visit - Week 60 Visit	5.0	2.5
Week 60 Visit - Week 64 Visit	5.0	2.5
Week 68 Visit - Week 72 Visit	5.0	2.5
Week 72 Visit - Week 76 Visit	5.0	2.5
Subjects with data up to Week 52, n	60	61
Median dose (Mg/day)		
Double-blind period		
Optimised dose (Baseline)	12.5	10.0
Week 0 Visit - Week 4 Visit	12.5	10.0
Week 4 Visit - Week 8 Visit	10.0	9.1
Week 8 Visit - Week 12 Visit	10.0	5.5
Week 12 Visit - Week 16 Visit	10.0	5.3
Week 16 Visit - Week 20 Visit	10.0	5.0
Week 20 Visit - Week 24 Visit	10.0	2.5
Open-label period	10.0	2.5
Week 24 Visit - Week 28 Visit	8.5	3.8
Week 28 Visit - Week 32 Visit	7.5	4.0
Week 32 Visit - Week 36 Visit	6.8	2.5
Week 36 Visit - Week 40 Visit	6.2	2.8
Week 40 Visit - Week 44 Visit	5.0	2.6
Week 44 Visit - Week 48 Visit	5.0	3.1

Week 48 Visit - Week 52 Visit		

4.11.6.4 Lung function

COSMOS – At the time of the first assessment of lung function (Week 16) and continuing through the conclusion of the study, subjects previously treated with placebo showed increases from baseline in pre-bronchodilator FEV1 (

Table 85). As expected, little change was observed in subjects previously treated with mepolizumab.

Table 85 Summary of Pre-Bronchodilator FEV1 (mL) by treatment within MENSA and SIRIUS (COSMOS, AT Population)

	Mepolizumab 100 mg SC		
Pre-bronchodilator FEV_1 (ml)	**Previous Placebo (N=237)**	**Previous Mepolizumab (N=414)**	**All Subjects (N=651)**
Baseline			
FEV_1, n	237	412	649
Mean (SD)	1957 (667.8)	2010 (733.1)	1991 (709.9)
Median (Min, Max)	1880 (450, 4650)	1920 (480, 4780)	1910 (450, 4780)
Week 16			
FEV_1, Change from Baseline, N	232	400	632
Mean (SD)	155 (383.7)	15 (340.2)	67 (362.7)
Median (Min, Max)	110 (-970, 1870)	-5 (-1310, 1460)	30 (-1310, 1870)
Week 28			
FEV_1, Change from Baseline, N	229	386	615
Mean (SD)	115 (451.1)	12 (378.7)	50 (409.8)
Median (Min, Max)	89 (-1950, 2540)	5 (-1660, 1760)	30 (-1950, 2540)
Week 52			
FEV_1, Change from Baseline, N	223	379	602
Mean (SD)	100 (447.5)	-13 (374.1)	29 (406.2)
Median (Min, Max)	50 (-1210, 2460)	-10 (-1580, 1400)	20 (-1580, 2460)

COLUMBA – Beginning at first time point measured after treatment initiation (Week 12) and continuing through Week 48, subjects showed mean increases from baseline in pre-bronchodilator FEV_1 at each assessment (Table 86).

Table 86 Summary of Pre-Bronchodilator FEV_1 (mL) (COLUMBA, AT Population)

Pre-bronchodilator FEV_1 (ml)	**Mepolizumab 100 mg SC (N=347)**
Baseline, n	347
Mean (SD)	1811 (696.2)
Median (Min, Max)	1650 (510, 3990)
Week 12 Change from Baseline, N	340
Mean (SD)	124 (346.9)
Median (Min, Max)	90 (-740, 1720)
Week 24 Change from Baseline, N	334
Mean (SD)	144 (335.0)
Median (Min, Max)	105 (-950, 1270)
Week 48 Change from Baseline, N	315
Mean (SD)	91 (395.1)
Median (Min, Max)	60 (-1620, 1810)

In COLUMBA, the baseline mean percent predicted FEV_1 of 60% was consistent with the mean baseline value in DREAM. Mean improvements in pre-bronchodilator FEV_1 of 91 to 144 mL were observed showing an overall improvement in lung function.

4.11.6.5 Asthma Control Questionnaire (ACQ-5)

COSMOS – At the time of the first assessment (Week 4) and continuing through to Week 52, subjects previously treated with placebo showed decreases (improvements) from baseline in ACQ-5 scores as shown in Table 87 below. In subjects, previously treated with mepolizumab, improvements achieved following mepolizumab treatment within previous studies MENSA and SIRIUS, were sustained.

Table 87 Summary of Asthma Control Questionnaire (ACQ-5) Score by Treatment within MENSA or SIRIUS (COSMOS, AT Population)

	Mepolizumab 100 mg SC		
ACQ-5 Score	**Previous Placebo (N=237)**	**Previous Mepolizumab (N=414)**	**All Subjects (N=651)**
Baseline, n	220	390	610
Mean (SD)	1.76 (1.127)	1.25 (1.102)	1.44 (1.136)
Median (Min, Max)	1.60 (0.0, 5.2)	1.00 (0.0, 6.0)	1.20 (0.0, 6.0)
Week 4 Change from Baseline, N	218	385	603
Mean (SD)	-0.28 (0.883)	0.01 (0.751)	-0.09 (0.812)
Median (Min, Max)	-0.20 (-3.4, 2.6)	0.00 (-3.0, 3.6)	0.00 (-3.4, 3.6)
Week 16 Change from Baseline, N	215	377	592
Mean (SD)	-0.46 (0.911)	0.09 (0.867)	-0.11 (0.920)
Median (Min, Max)	-0.40 (-3.6, 3.0)	0.000 (-2.6, 4.2)	0.00 (-3.6, 4.2)
Week 28 Change from Baseline, N	212	365	577
Mean (SD)	-0.33 (1.097)	0.12 (0.936)	-0.05 (1.021)
Median (Min, Max)	-0.20 (-3.0, 3.6)	0.00 (-2.8, 4.6)	0.00 (-3.0, 4.6)
Week 40 Change from Baseline, N	210	354	564
Mean (SD)	-0.30 (1.026)	0.03 (0.869)	-0.10 (0.944)
Median (Min, Max)	-0.20 (-3.8, 3.8)	0.00 (-3.4, 3.8)	0.00 (-3.8, 3.8)
Week 52 Change from Baseline, N	206	350	556
Mean (SD)	-0.30 (0.996)	0.04 (0.965)	-0.09 (0.990)
Median (Min, Max)	-0.20 (-3.8, 2.6)	0.00 (-4.0, 4.0)	0.00 (-4.0, 4.0)
Follow up change from Baseline, N	142	196	338
Mean (SD)	0.05 (1.191)	0.31 (1.078)	0.20 (1.132)
Median (Min, Max)	0.00 (-2.8, 4.8)	0.10 (-3.0, 3.6)	0.00 (-3.0, 4.8)

COLUMBA – Beginning at the first time point measured after treatment initiation (Week 12) and continuing through Week 60, subjects treated with mepolizumab showed decreases (improvements) from baseline in ACQ-5 scores as shown in Table 88 below. The mean changes from baseline in ACQ-5 score were greater that the minimal clinically important difference (MCID) of 0.5 at Weeks 24, 36, 48 and 60.

Table 88 Summary of Asthma Control Questionnaire (ACQ-5) Change from Baseline (COLUMBA, AT Population)

ACQ-5 Score	Mepolizumab 100 mg SC (N=347)
Baseline, n	346
Mean (SD)	2.21 (1.17)
Median (Min, Max)	2.20 (0.0, 5.4)
Week 12 Change from Baseline, N	341
Mean (SD)	-0.47 (0.99)
Median (Min, Max)	-0.40 (-4.4, 2.2)
Week 24 Change from Baseline, N	335
Mean (SD)	-0.55 (1.04)
Median (Min, Max)	-0.40 (-4.6, 4.0)
Week 36 Change from Baseline, N	327
Mean (SD)	-0.56 (1.09)
Median (Min, Max)	-0.40 (-4.0, 3.0)
Week 48 Change from Baseline, N	314
Mean (SD)	-0.55 (1.10)
Median (Min, Max)	-0.40 (-4.2, 3.4)
Week 60 Change from Baseline, N	85
Mean (SD)	-0.62 (1.22)
Median (Min, Max)	-0.40 (-4.2, 1.8)

4.11.6.6 Blood eosinophils

COSMOS - The geometric mean eosinophil counts for subjects who were previously treated with placebo were reduced from 280 cells/μL (at baseline) to 50 to 60 cells/μL at most other time points. As expected, for subjects who previously received mepolizumab, overall values were unchanged during the current study.

Mepolizumab produced a sustained reduction of blood eosinophils through the duration of treatment providing evidence for no tolerance with mepolizumab SC treatment. The suppression of blood eosinophils in the current study was consistent with that measured in the MENSA and SIRIUS.

COLUMBA - Blood eosinophil measurements during treatment showed a decrease of approximately 80% at all time points, therefore also showing a sustained reduction of blood eosinophils through the duration of treatment to date.

Further details of all efficacy results can be found in the CSRs.

4.11.7 Adverse events and immunogenicity

The safety and immunogenicity of the non-RCT studies have been summarised in section 4.12.

4.11.8 Conclusion

During open-label treatment of all subjects treated with mepolizumab in COSMOS, the rates of exacerbations per year remained low in the subjects who were previously treated with mepolizumab (0.92 for Weeks 32 to 52 and 0.92 for Weeks 52 to 84). These data indicate that the effect of mepolizumab on the reduction of exacerbations is durable and stable over time. The use of OCS also remained low in

the subjects who were previously treated with mepolizumab (2.5 mg/day for Weeks 44 to 76). These data also indicate that the effect of mepolizumab on the reduction of OCS use is also durable and stable over time.

In patients that were previously on placebo for 32 and 24 weeks (MENSA and SIRIUS, respectively), the addition of mepolizumab 100mg SC to their SOC resulted in a significant reduction in exacerbations. In MENSA, the rate of exacerbations per year for the subjects previously treated with placebo and switched to mepolizumab decreased over time in COSMOS (from 1.94 to 1.04/year) despite an initial reduction of the exacerbation rate on placebo for 32 weeks (MENSA, from 3.6 to 1.74/year). Patients previously treated with placebo in SIRIUS also experienced an initial reduction in exacerbation rate (2.9 to 2.12/year). When switched to mepolizumab there was a reduction in rate of exacerbations from 2.2 to 1.13 per year.
When looking at the combined MENSA and SIRIUS population, when mepolizumab was started in previous placebo users, there was an overall combined reduction to 0.99 exacerbations per year. The use of OCS for the subjects who were previously treated with placebo in SIRIUS and switched to mepolizumab also decreased over time during COSMOS (from 10.0 to 5.0 mg/day). An improvement could also be seen in lung function and ACQ-5 scores in this particular subject group.

4.12 Adverse reactions

As per NICE submission guidance we aim to provide an overview of the comparative RCTs and regulatory summary for EMA. However, we will concentrate on the safety results of the severe asthma population, more specifically drug-related adverse events (AE). Full details are found in the Integrated Safety Summary submitted to the EMA.

The assessment of safety of mepolizumab has been based on safety results of the following studies, highlighted in Section 4.2:

- Placebo-controlled Severe Asthma Studies MEA112997 (DREAM[36,114]), MEA115588 (MENSA[16,115]) and MEA115575 (SIRIUS[51,55])
- Open-label extension studies MEA115661 (COSMOS[140]) and MEA115666 (COLUMBA[141]).

All studies except for COLUMBA have been completed and CSR are available. For COLUMBA, an interim CSR is available. Study methodologies for RCTs are provided in Section 4.3 (Section 4.10 for OLEs), and a summary of patient demographics, disposition, and quality assessments for each study is provided in Sections 4.5 and 4.6 (Section 4.10 for OLEs).

4.12.1 Common adverse events

Common AEs were defined as those which occurred in ≥3% of subjects in a given treatment group.

4.12.1.1 Placebo-controlled severe asthma studies

The incidence of AEs in the severe asthma studies were similar for the placebo group (82%) compared with the mepolizumab 100 mg SC group (79%), and the mepolizumab 75 mg IV group (83%).

The incidence of injection site reactions with mepolizumab 100 mg SC and placebo was 8% and 3%, respectively. These events were all non-serious, mild to moderate in intensity and the majority resolved within a few days. The common symptoms reported with these events included pain, erythema, swelling, itching, and burning sensation. Two patients withdrew due to injection site reactions.

Table 88 provides the proportion of subjects experiencing the most common on-treatment AEs pooled across the PCSA studies and the corresponding event rates adjusted for exposure (frequency of events per 1000 subject-years of exposure).

Table 89: Summary of Most Frequent On-Treatment Adverse Events Reported by 3% or More of Subjects in Any Treatment Group (CMH Adjusted) (PCSA Studies)

Event	Treatment	N	Number (%) with Event		Adjusted Cumulative Proportion [1]	Relative Risk	(95% CI) [2]
Eczema	Placebo	412	2	0.50%	0.50%		
	All Doses	915	23	2.50%	2.60%	5.34	(1.25, 22.78)
Nasal congestion	Placebo	412	4	1.00%	1.00%		
	All Doses	915	24	2.60%	2.50%	2.62	(0.89, 7.72)
Dyspnoea	Placebo	412	4	1.00%	1.10%		
	All Doses	915	23	2.50%	2.30%	2.2	(0.78, 6.20)
Rhinitis allergic	Placebo	412	7	1.70%	1.70%		
	All Doses	915	27	3.00%	2.80%	1.64	(0.70, 3.85)
Urinary tract infection	Placebo	412	9	2.20%	2.10%		
	All Doses	915	32	3.50%	3.40%	1.63	(0.77, 3.47)
Pharyngitis	Placebo	412	8	1.90%	2.00%		
	All Doses	915	25	2.70%	2.70%	1.34	(0.61, 2.97)
Abdominal pain upper	Placebo	412	8	1.90%	2.00%		
	All Doses	915	24	2.60%	2.60%	1.32	(0.59, 2.95)
Pyrexia	Placebo	412	9	2.20%	1.90%		
	All Doses	915	22	2.40%	2.50%	1.29	(0.57, 2.94)
Back pain	Placebo	412	20	4.90%	5.00%		
	All Doses	915	60	6.60%	6.30%	1.26	(0.77, 2.06)
Infusion related reaction	Placebo	412	11	2.70%	2.90%		
	All Doses	915	40	4.40%	3.70%	1.24	(0.65,2.38)
Injection site reaction	Placebo	412	13	3.20%	3.20%		
	All Doses	915	31	3.40%	3.80%	1.2	(0.64,2.23)
Headache	Placebo	412	74	18.00%	17.80%		
	All Doses	915	195	21.30%	21.30%	1.2	(0.94,1.53)
Gastroenteritis	Placebo	412	9	2.20%	2.30%		
	All Doses	915	24	2.60%	2.70%	1.2	(0.57,2.52)
Lower respiratory tract	Placebo	412	10	2.40%	2.40%		
	All Doses	915	25	2.70%	2.80%	1.14	(0.55,2.37)
Influenza	Placebo	412	15	3.60%	3.80%		
	All Doses	915	37	4.00%	4.00%	1.06	(0.59,1.89)
Fatigue	Placebo	412	17	4.10%	4.00%		

	All Doses	915	35	3.80%	4.10%	1.04	(0.59,1.84)
Nasopharyngitis	Placebo	412	80	19.40%	19.40%		
	All Doses	915	184	20.10%	19.80%	1.02	(0.80,1.30)
Arthralgia	Placebo	412	23	5.60%	5.60%		
	All Doses	915	50	5.50%	5.60%	0.99	(0.61,1.61)
Rhinitis	Placebo	412	12	2.90%	3.00%		
	All Doses	915	25	2.70%	2.90%	0.96	(0.50, 1.84)
Hypertension	Placebo	412	12	2.90%	3.00%		
	All Doses	915	28	3.10%	2.90%	0.95	(0.49, 1.85)
Pain in extremity	Placebo	412	16	3.90%	3.90%		
	All Doses	915	32	3.50%	3.60%	0.9	(0.50, 1.62)
Dizziness	Placebo	412	13	3.20%	3.00%		
	All Doses	915	25	2.70%	2.70%	0.9	(0.45, 1.80)
Upper respiratory tract	Placebo	412	47	11.40%	11.50%		
	All Doses	915	96	10.50%	10.30%	0.9	(0.64, 1.25)
Bronchitis	Placebo	412	39	9.50%	9.50%		
	All Doses	915	73	8.00%	7.90%	0.83	(0.57, 1.21)
Sinusitis	Placebo	412	40	9.70%	9.80%		
	All Doses	915	68	7.40%	7.60%	0.78	(0.54, 1.13)
Oropharyngeal pain	Placebo	412	27	6.60%	6.40%		
	All Doses	915	45	4.90%	5.00%	0.77	(0.48, 1.24)
Nausea	Placebo	412	17	4.10%	3.80%		
	All Doses	915	26	2.80%	3.00%	0.77	(0.41, 1.44)
Cough	Placebo	412	21	5.10%	5.30%		
	All Doses	915	41	4.50%	4.10%	0.77	(0.46, 1.29)
Hypersensitivity	Placebo	412	11	2.70%	2.60%		
	All Doses	915	18	2.00%	2.00%	0.76	(0.35, 1.64)
Myalgia	Placebo	412	12	2.90%	3.00%		
	All Doses	915	19	2.10%	2.10%	0.69	(0.34, 1.41)
Asthma	Placebo	412	61	14.80%	14.90%		
	All Doses	915	89	9.70%	9.10%	0.61	(0.45, 0.84)
Oedema peripheral	Placebo	412	13	3.20%	3.20%		
	All Doses	915	14	1.50%	1.70%	0.52	(0.25, 1.07)
Diarrhoea	Placebo	412	19	4.60%	4.60%		
	All Doses	915	21	2.30%	2.20%	0.47	(0.25, 0.88)

Note: Studies included: DREAM, MENSA and SIRIUS. [1] Adjusted using Cochran-Mantel-Haenszel weights [2] Calculated using the Cochran-Mantel-Haenszel method

All other relative risks were less than 2. Of the 33 events reported by 3% or more of subjects, 17 were reported more frequently with mepolizumab and 16 were reported more frequently with placebo (

Table 89).

4.12.1.2 Open-label Extension Severe Asthma Studies

Similar to that seen with the Severe Asthma Studies, nasopharyngitis (23%) and headache (14%) were the most frequently reported AEs in the OLE Studies, COSMOS and COLUMBA.

When looking at data from the completed COSMOS study alone, it can be seen that the most frequently reported AEs remained nasopharyngitis (30%) and headache (14%), but also included upper respiratory tract infection (16%) and asthma (exacerbating) (14%) as shown in Table 90 below.

Table 90: Summary of Most Frequent (≥3) On-Treatment Averse Events (COSMOS, AT Population, Final report)

Adverse Event (Preferred Term)	Number (%) Subjects		
	Mepolizumab 100 mg SC		
	Previous Placebo (N=237)	Previous Mepolizumab (N=414)	All Subjects (N=651)
Any event	200 (84)	358 (86)	558 (86)
Nasopharyngitis	82 (35)	114 (28)	196 (30)
Upper respiratory tract infection	40 (17)	61 (15)	101 (16)
Asthma[1]	36 (15)	54 (13)	90 (14)
Headache	28 (12)	60 (14)	88 (14)
Bronchitis	34 (14)	46 (11)	80 (12)
Sinusitis	23 (10)	43 (10)	66 (10)
Back pain	18 (8)	28 (7)	46 (7)
Arthralgia	17 (7)	27 (7)	44 (7)
Oropharyngeal pain	11 (5)	23 (6)	34 (5)
Injection site reaction	15 (6)	14 (3)	29 (4)
Influenza	12 (5)	16 (4)	28 (4)
Nausea	11 (5)	16 (4)	27 (4)
Cough	8 (3)	18 (4)	26 (4)
Lower respiratory tract infection	11 (5)	15 (4)	26 (4)
Fatigue	7 (3)	17 (4)	24 (4)
Rhinitis	8 (3)	15 (4)	23 (4)
Diarrhoea	12 (5)	10 (2)	22 (3)
Urinary tract infection	8 (3)	14 (3)	22 (3)
Musculoskeletal pain	11 (5)	10 (2)	21 (3)
Pain in extremity	6 (3)	15 (4)	21 (3)
Dizziness	8 (3)	11 (3)	19 (3)
Myalgia	8 (3)	11 (3)	19 (3)
Gastroenteritis	8 (3)	9 (2)	17 (3)
Pyrexia	9 (4)	8 (2)	17 (3)

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

In COLUMBA, the most frequently reported AEs during the treatment period were nasopharyngitis (26%), headache (21%), upper respiratory tract infection (13%), and asthma (worsening) (11%).

4.12.2 Adverse Events of Special Interest

Adverse events of special interest were systemic (non-allergic and allergic/hypersensitivity) and local site reactions, cardiac events, infections, and malignancies.

The CMH-adjusted relative risk for all doses of mepolizumab combined compared with placebo and mepolizumab 100 mg SC and 75 mg IV combined (mepolizumab 100 mg SC/75 mg IV) compared with placebo can be seen in Appendix 8.8.

In the Severe Asthma Studies, all infections (including serious and opportunistic) were reported most frequently but occurred at a similar incidence in the placebo group (58%) compared with the mepolizumab 100 mg SC/75 mg IV combined group and all doses of mepolizumab combined group (57%, each).

Systemic reactions and local site reactions were the next most frequent and occurred at a similar incidence in the placebo group (5% and 3%, respectively) compared with the mepolizumab 100 mg SC/75 mg IV combined group (3% and 5%,

respectively) and the all doses of mepolizumab combined group (6% and 3%, respectively). There were no reports of anaphylaxis by investigators following a protocol-required assessment against the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) Second Symposium on Anaphylaxis.[142] Also no evidence of anaphylaxis was found in a retrospective review of all reports of systemic reactions conducted by GSK.

The final COSMOS safety data showed that 13 subjects (2%) experienced investigator-defined systemic reactions, which included injection related/non-allergic reaction (7 subjects; 1%) and hypersensitivity/allergic (4 subjects, <1%). Overall, it can be seen the risk of these reactions was low.

A total of 29 subjects (4%) experienced local injection site reactions, all of which were non-serious and the majority of mild to moderate intensity with resolution. This was consistent with the results observed in MENSA and SIRIUS.

Infections were reported for 455 subjects (70%). The most common (≥10%) infections were nasopharyngitis (196 subjects, 30%), upper respiratroy tract infection (101 subjects, 16%), bronchitis (80 subjects, 12%), and sinusitis (66 subjects, 10%). Serious infections were reported for 26 subjects (4%) and included pneumonia (4 subjects, <1%), which was the most common. The results were also similar to those observed in the original studies, MENSA and DREAM.

4.12.3 Drug related adverse events

The incidence of drug-related AEs in the PCSA studies was 16% in the placebo group compared with 23% in the mepolizumab 100 mg SC group and 18% in the mepolizumab 75 mg IV group (Table 91). The incidence of drug-related AEs was similar for the other mepolizumab treatment groups. The most frequently reported drug-related AEs in the placebo and mepolizumab 100 mg SC and 75 mg IV groups were headache (2%, 5%, and 3%, respectively) and injection site reaction (3%, 6%, and 2%, respectively).

Table 91: Most Frequent (≥5 Subjects Across Treatment Groups) Drug- Related[1] Adverse Events (PCSA studies, Safety Population)

Drug-Related Adverse Event (Preferred Term)	Number (%) of Subjects					
		Mepolizumab				
	Placebo N=412	100 SC N=263	75 IV N=344	250 IV N=152	750 IV N=156	All Doses N=915
Any Drug-related AE	67 (16)	60 (23)	61 (18)	29 (19)	33 (21)	183 (20)
Infusion-related reaction[2]	11 (3)	0	8 (2)	12 (8)	19 (12)	39 (4)
Headache	10 (2)	13 (5)	11 (3)	6 (4)	5 (3)	35 (4)
Injection site reaction	12 (3)	17 (6)	8 (2)	0	0	25 (3)
Fatigue	5 (1)	5 (2)	4 (1)	2 (1)	0	11 (1)
Hypersensitivity	6 (1)	3 (1)	2 (<1)	1 (<1)	2 (1)	8 (<1)
Nausea	7 (2)	3 (1)	0	2 (1)	0	5 (<1)
Arthralgia	2 (<1)	2 (<1)	2 (<1)	1 (<1)	2 (1)	7 (<1)
Dizziness	1 (<1)	4 (2)	0	1 (<1)	1 (<1)	6 (<1)
Myalgia	2 (<1)	2 (<1)	1 (<1)	1 (<1)	1 (<1)	5 (<1)
Oedema peripheral	3 (<1)	0	3 (<1)	0	0	3 (<1)
Hypertension	3 (<1)	0	1 (<1)	2 (1)	0	3 (<1)
Injection-related reaction	3 (<1)	3 (1)	0	0	0	3 (<1)

Migraine	1 (<1)	2 (<1)	0	0	2 (1)	4 (<1)
Vomiting	2 (<1)	1 (<1)	1 (<1)	1 (<1)	0	3 (<1)
Exposure Adjusted[3]						
Drug-Related Adverse Event (Preferred Term)		**Mepolizumab**				
	Placebo Subj Yrs = 284	**100 SC Subj Yrs = 147**	**75 IV Subj Yrs = 254**	**250 IV Subj Yrs = 142**	**750 IV Subj Yrs = 144**	**All Doses Subj Yrs = 687**
Infusion-related reaction[2]	73.9	0	55.1	239.1	383.3	149.8
Injection site reaction	95.1	183.1	39.3	0	0	53.8
Headache	52.8	162.7	82.6	56.3	97.6	97.5
Fatigue	17.6	47.5	15.7	14.1	0	18.9
Hypersensitivity	56.3	20.3	23.6	7.0	13.9	17.5
Nausea	31.7	67.8	0	21.1	0	18.9
Arthralgia	7.0	13.6	7.9	7.0	20.9	11.6
Dizziness	3.5	40.7	0	7.0	7.0	11.6
Myalgia	10.6	13.6	3.9	7.0	7.0	7.3
Oedema peripheral	14.1	0	11.8	0	0	4.4
Hypertension	10.6	0	3.9	14.1	0	4.4
Injection-related reaction	14.1	33.9	0	0	0	7.3
Migraine	3.5	20.3	0	0	20.9	8.7
Vomiting	10.6	6.8	3.9	7.0	0	4.4

Note: Studies included: DREAM, MENSA, and SIRIUS 1. As assessed by the investigator 2. Preferred Term was only reported from studies where an IV formulation was used 3. Numbers represent the frequency of events per 1000 subject-years of exposure

Consistent with that seen in the PCSA studies, injection site reaction and headache were the most frequently reported drug-related AEs in the OLE Studies. The final COSMOS study results are shown below in Table 92.

Table 92: Drug-related Adverse Events Occurring in More than One Subject (COSMOS, AT Population, Final report)

	Number (%) Subjects		
	Mepolizumab 100 mg SC		
Drug-Related Adverse Event[1] (Preferred Term)	**Previous Placebo (N=237)**	**Previous Mepolizumab (N=414)**	**All Subjects (N=651)**
Any event	46 (19)	73 (18)	119 (18)
Injection site reaction	15 (6)	12 (3)	27 (4)
Headache	5 (2)	12 (3)	17 (3)
Arthralgia	3 (1)	7 (2)	10 (2)
Injection related reaction	5 (2)	2 (<1)	7 (1)
Fatigue	1 (<1)	5 (1)	6 (<1)
Diarrhea	1 (<1)	3 (<1)	4 (<1)
Hypersensitivity	1 (<1)	3 (<1)	4 (<1)
Nasopharyngitis	1 (<1)	3 (<1)	4 (<1)
Nausea	2 (<1)	2 (<1)	4 (<1)
Type IV hypersensitivity reaction	2 (<1)	2 (<1)	4 (<1)
Upper respiratory tract infection	1 (<1)	3 (<1)	4 (<1)
Asthenia	1 (<1)	2 (<1)	3 (<1)
Bronchitis	0	3 (<1)	3 (<1)
Dizziness	3 (1)	0	3 (<1)
Alanine aminotransferase increased	1 (<1)	1 (<1)	2 (<1)
Gastroenteritis	1 (<1)	1 (<1)	2 (<1)
Hypercholesterolaemia	0	2 (<1)	2 (<1)
Hyperhidrosis	1 (<1)	1 (<1)	2 (<1)
Influenza	1 (<1)	1 (<1)	2 (<1)
Influenza like illness	0	2 (<1)	2 (<1)
Nasal congestion	1 (<1)	1 (<1)	2 (<1)
Pain congestion	1 (<1)	1 (<1)	2 (<1)
Peripheral swelling	2 (<1)	0	2 (<1)

Tremor	1 (<1)	1 (<1)	2 (<1)
Urticaria	0	2 (<1)	2 (<1)
Vomiting	1 (<1)	1 (<1)	2 (<1)

1. Investigator's judgement of causality.

4.12.4 Post treatment adverse events

AEs with a start date greater than 4 weeks after the last dose of medication were classified as post-treatment AEs.

Studies MENSA and SIRIUS had a post-treatment follow-up period for subjects who did not enrol in the OLE study (approximately 6% of total population) during which AEs were reported. Only 4% of subjects treated with mepolizumab 100 mg SC who had follow-up visits in these two studies reported a post-treatment AE. In DREAM, post-treatment AEs occurred in 26 subjects (20%) in the mepolizumab 75 mg IV group, 30 subjects (23%) in the mepolizumab 250 mg IV group, 32 subjects (25%) in the mepolizumab 750 mg IV group, and 36 subjects (29%) in the placebo group (DREAM CSR, Table 7.16), which was relatively consistent with AEs that occurred during the trial.

In the final COSMOS study read out, post-treatment AEs were reported for 107 subjects (16%). Asthma was the only SAE reported in more than 1 subject.

4.12.5 Evaluation of long-term safety

In order to determine if there were differences in the AE profile as time on treatment increased and to identify the occurrence of new AEs that could be associated with increased exposure to study drug, the profiles of AEs with an onset of 0 to <12 weeks, 12 to <24 weeks, 24 to <36 weeks, 36 to <48 weeks and ≥48 weeks were compared.

With long-term mepolizumab treatment, reports of most AEs tended to decrease as time on treatment increased. There was no pattern of occurrence that would suggest a difference in the AE profile with longer exposure to study medication.

4.12.6 Serious adverse events

4.12.6.1 Placebo-controlled severe asthma studies

A total of 155 subjects in the PCSA studies reported SAEs; 15% in the placebo group, 6% in the mepolizumab 100 mg SC group, and 10% in the mepolizumab 75 mg IV group (

Table **93**). The incidence of SAEs in the mepolizumab groups was similar to or less than the placebo group for all other SAEs.

Table 93 On-Treatment Serious Adverse Events occurring in more than one subject (PCSA Studies, Safety Population)

Serious Adverse Event (Preferred Term)	Number (%) Subjects	
		Mepolizumab

	Placebo N=412	100 SC N=263	75 IV N=344	250 IV N=152	750 IV N=156	All Doses N=915
Any SAE	63 (15)	17 (6)	34 (10)	23 (15)	18 (12)	92 (10)
Asthma	38 (9)	5 (2)	20 (6)	15 (10)	9 (6)	49 (5)
Pneumonia	3 (<1)	1 (<1)	1 (<1)	0	2 (1)	4 (<1)
Nephrolithiasis	3 (<1)	1 (<1)	0	0	0	1 (<1)
Bronchitis	2 (<1)	0	1 (<1)	0	0	1 (<1)
Lobar pneumonia	1 (<1)	0	2 (<1)	0	0	2 (<1)
Tendon rupture	1 (<1)	0	1 (<1)	0	1 (<1)	2 (<1)
Atrial flutter	1 (<1)	1 (<1)	0	0	0	1 (<1)
Cerebrovascular accident	2 (<1)	0	0	0	0	0
Herpes zoster	0	2 (<1)	0	0	0	2 (<1)
Hypersensitivity	1 (<1)	1 (<1)	0	0	0	1 (<1)
Hypertension	0	0	1 (<1)	0	1 (<1)	2 (<1)
Myocardial ischemia	0	0	1 (<1)	0	1 (<1)	2 (<1)
Viral upper respiratory tract infection	1 (<1)	0	1 (<1)	0	0	1 (<1)
Exposure Adjusted[1]						
		Mepolizumab				
Serious Adverse Event (Preferred Term)	**Placebo Subj Yrs = 284**	**100 SC Subj Yrs = 147**	**75 IV Subj Yrs = 254**	**250 IV Subj Yrs = 142**	**750 IV Subj Yrs = 144**	**All Doses Subj Yrs = 687**
Any SAE	**348.6**	**189.9**	**204.5**	**232.1**	**188.1**	**203.7**
Asthma	193.7	61.0	94.4	112.5	76.7	87.3
Pneumonia	10.6	6.8	3.9	0	13.9	5.8
Nephrolithiasis	10.6	6.8	0	0	0	1.5
Bronchitis	7.0	0	3.9	0	0	1.5
Lobar pneumonia	3.5	0	7.9	0	0	2.9
Tendon rupture	3.5	0	3.9	0	7.0	2.9
Atrial flutter	3.5	6.8	0	0	0	1.5
Cerebrovascular accident	7.0	0	0	0	0	0
Herpes zoster	0	13.6	0	0	0	2.9
Hypersensitivity	3.5	6.8	0	0	0	1.5
Hypertension	0	0	3.9	0	7.0	2.9
Myocardial ischemia	0	0	3.9	0	7.0	2.9
Viral upper respiratory tract infection	3.5	0	3.9	0	0	1.5

4.12.6.2 Open-label extension severe asthma studies

At the interim data cut-off point for both COLUMBA and COSMOS, a total of 83 subjects treated with mepolizumab 100 mg SC in the OLE Studies reported SAEs (8% and 9% in each study). Similar to that seen in the PCSA studies, the most frequent SAE was asthma, reported by 16 subjects (5%) in COLUMBA and 24 subjects (4%) in COSMOS at the time of the interim report.

The incidence (both percent and exposure-adjusted) and pattern of SAEs assessed were similar to each other and to the overall population in the OLE Studies.

At completion of the COSMOS study, the results showed there were a total of 94 subjects (14%) that experienced SAEs during the on-treatment period. The most common SAE was asthma, which occurred in 38 subjects (6%). Pneumonia (4 subjects), atrial fibrillation (3 subjects), appendicitis, bronchitis, diverticulitis, and upper respiratory tract infection (2 subjects each) were the only other SAEs that occurred in more than 1 subject (<1%). Only two subjects had a SAE that was considered possibly related to study drug by the investigator (Subject MEA115588.2838, spontaneous abortion; Subject MEA115575.1497, Type IV hypersensitivity reaction, see CSR for patient narrative).

4.12.6.3 Deaths

A total of 9 deaths have been reported in the severe asthma studies (PCSA studies, n=5) and OLE Studies (n=4): In the PCSA studies 2 patients (<1%) were receiving placebo (1. road traffic accident and 2. aspiration secondary due to gastrointestinal haemorrhage) and 3 patients (<1%) were receiving mepolizumab (1. severe acute pancreatitis and septic shock, 2. severe acute asthma exacerbation, 3. asphyxia due to suicide by hanging in 1 subject). In the OLE studies (data cut of 23rd September 2015, as COLUMBA still ongoing) there were 4 deaths with all patients receiving mepolizumab (1. due to respiratory arrest, 2. complications due to morbid obesity, 3. myocardial infarction and 4. acute heart failure). 3 deaths were linked to the patients' underlying asthma. None of the deaths were considered related to study medication by the investigator.

4.12.7 Adverse events leading to withdrawal

For adverse events that led to the withdrawal of subjects from the studies, please refer to Section 4.5 for the PCSA studies, and Section 4.11 for the OLE studies.

4.12.8 Immunogenicity

As per EMA: 'Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment. In the placebo-controlled trials, 15/260 (6%) of subjects treated with 100 mg dose subcutaneously developed anti-mepolizumab antibodies after having received at least one dose of mepolizumab. Neutralising antibodies were detected in one subject. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level.'

In addition, in the OLE studies, COSMOS and COLUMBA, all 646 and 347 subjects, respectively treated with mepolizumab 100mg SC were tested for the presence of anti-mepolizumab antibodies. At the point of final read out, a total of 31 subjects (5%, 13th May 2015) and 18 (5%, 28th February 2014), respectively had confirmed positive anti-mepolizumab antibody results for at least one visit after Baseline. None of the subjects tested positive in the neutralising antibody assay.

4.12.9 Adverse events listed in SmPC

Table 94 SmPC tabulated list of Adverse Events

System Organ Class	Adverse Reactions	Frequency
Infections &infestations	Lower respiratory tract infections Urinary tract infection Pharyngitis	Common
Immune system disorders	Hypersensitivity reactions (systemic allergic)	Common
Nervous system disorders	Headache	Very common
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Common
Gastrointestinal disorders	Abdominal pain upper	Common
Skin and subcutaneous tissue disorders	Eczema	Common
Musculoskeletal and connective tissue disorders	Back pain	Common
General disorders and administration site conditions	Administration-related reactions (systemic non allergic) Local injection site reaction Pyrexia	Common

4.12.10 Conclusion

This safety summary demonstrates that mepolizumab is well tolerated in severe refractory eosinophilic asthma patients receiving optimised standard of care. The safety profile is similar to subjects receiving placebo added to optimised standard of care, with the exception of an increased rate of local site reactions with mepolizumab. While the certainty of the safety profile of any medicine is limited to the breadth of exposure studies, the data do not suggest evidence of a differential treatment response across subject subgroups.

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Statement of principle findings

The primary benefits of mepolizumab treatment can be classified as (1) reduction/ elimination of exacerbations and (2) reducing dependence on daily doses of systemic corticosteroids, which are associated with both untoward short- and long-term adverse events, while maintaining or improving overall asthma control. This is also reflected in the demonstrated improvements in quality of life when treated with add-on mepolizumab. Chronic inflammation and exacerbations are thought to be associated with an increased risk of permanent damage to the lung tissue or remodelling changes.[143] Thus, it is paramount to control inflammation and reduce exacerbations in patients at high risk. Mepolizumab specifically targets such a high risk patient population and reduces exacerbations.

GSK proposed population

Mindful of NHS resources GSK have identified a more severe population within the licensed population with an enhanced potential for clinical benefit and hence likely to

provide a more cost effective use of NHS resources. The population have been identified taking into account the clinical trial population (severe refractory eosinophilic asthma patients at step 4 or 5 of the BTS/SIGN treatment algorithm), the clinical trial results presented in section 4.7 and clinical specialists' opinion:

Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/µl at initiation of treatment; and ≥4 exacerbations in the previous year or dependency on systemic corticosteroids (maintenance OCS).

This patient population exists in the UK and is readily identifiable in current clinical practice as part of current severe asthma assessment standards. In addition, the blood eosinophil count, for identification of patients likely to respond to mepolizumab, is taken as part of routine patient assessment. By selecting patients with ≥4 exacerbations in the past year or dependency on mOCS, it is also consistent with the current NICE guidance for omalizumab.

1. In the GSK proposed population a reduction in rate of exacerbations was observed compared to standard of care by 50% (p=0.002) and 60% (p<0.001) of patients in both 100mg SC and 75mg IV arm, respectively. If patients on maintenance OCS with <4 exacerbations were excluded from the population the reduction was 61% (p<0.001) Section 4.7.4.1). This exceeded a clinically meaningful reduction in exacerbations of 30% despite being a more severe asthma population.

> The GSK proposed population showed a higher reduction in clinically significant exacerbations than seen for the ITT population (ITT: 47% [p<0.001] and 53% [p<0.001], Section 4.7.5.1).

2. The reduction in exacerbations resulted in a reduction in emergency department visits +/- hospitalisation

> The GSK proposed population had a reduction in the rate of Exacerbations Requiring Emergency Department Visits and Hospitalisation compared to Standard of Care by 51% (p=0.157) and 69% (p=0.048) in the 100mg SC and 75mg IV, respectively. The GSK proposed population excluding mOCS users with <4 exacerbations showed the same trend (55% (p=0.177) and 79% (p=0.033) for the 100mg SC and 75mg IV doses respectively; Section 4.7.4.2).
>
> The same trend was observed in the Rate of Exacerbations Requiring Hospitalisation with a reduction of 45% (p=0.372) and 72% (p=0.129) in the GSK proposed population and 51% (p=0.388) and 81% (p=0.19) in the GSK proposed population excluding mOCS users with <4 exacerbations in the 100mg SC and 75mg IV arm, respectively (Section 4.7.4.2).
>
> Due to the small number of events generally observed, statistical significance was not reached in this subgroup (Section 4.7.4.2).

3. The GSK proposed population had a statistically and clinically significant improvement in SGRQ score by -10 units (p<0.001) and -7.9 units (p=0.008) for

100mg SC and 75mg IV, respectively (MCID 4 units). When excluding the OCS users with <4 exacerbations the improvements were -12.8 units (p=0.009) and -9.9 units (p<0.001) for 100mg SC and 75mg IV, respectively (Section 4.7.4.3).

> This was an improvement by twice to almost triple the MCID and confirmed the additional benefit the GSK proposed population received over the ITT population (improvements of -7 and -6.4 units in the 100mg SC and 75mg IV groups respectively; [p<0.001], Section 4.7.5.3).

4. The GSK proposed population had a statistically and clinically significant improvement in ACQ vs. standard of care by -0.79 units (p<0.001) and 0.54 units (p<0.001) for 100mg SC and 75mg IV, respectively (MCID 0.5 units). When excluding mOCS users with <4 exacerbations the improvements were -0.96 (p<0.001) and -0.72 (p<0.001) in the 100mg SC and 75mg IV arms, respectively. (Section 4.7.4.4).

> These improvements exceed the MCID for ACQ of 0.5 in contrast to the ITT population results (0.44 and 0.42, p<0.001, Section 4.7.5.4). This provided further evidence that the selected subgroup had added benefit from add-on mepolizumab therapy.

5. The GSK proposed population showed a numerical reduction in OCS dose (OR 1.81, p=0.115, Section 4.7.4.6), while maintaining asthma control. However, the number of patients was reduced by this subgroup analysis, which meant that the analysis was not sufficiently powered and thus did not reach statistical significance.

> Around half of subjects treated with mepolizumab achieved at least a 50% reduction in OCS or to ≤5.0 mg (Section 4.7.4.6).
>
> Reassuringly, the fact that the subgroup identified a more severe asthma population is supported as the majority of patients who experienced a reduction in OCS use in the ITT population (ITT: OR 2.39, p=0.008, Section 4.7.5.5) were indeed represented in GSK proposed population (≥50% reduction: 26 of 37; ≤5mg: 27 of 37; 100% reduction: 7 of 10). This confirms that the GSK proposed population identified subjects that most benefit from add-on mepolizumab therapy.
>
> Asthma control showed the same trend in the GSK proposed population compared to the ITT population (Sections 4.7.4.6 & 4.7.5.5) and confirmed that mepolizumab add-on therapy achieved a reduction in OCS exposure while maintaining asthma control.

Thus, in the GSK proposed population, a more severe subgroup of patients, with add-on mepolizumab therapy demonstrated a reduction in rate of exacerbations; improvement in quality of life (SGRQ) and improvement in asthma control (ACQ) compared to standard of care that were greater than in the ITT population. By selecting this subgroup from the ITT population for analysis the number of subjects analysed was reduced and resulted in inadequate powering for robust statistical analysis for rarer events such as ED visits and hospitalisations. Yet a trend in reduction in ED visits and/or hospitalisations and OCS dose reduction aligned to that for the ITT population was observed.

Comparison to Omalizumab

The NMA showed that mepolizumab is associated with a significant reduction in clinically significant exacerbations versus omalizumab. The median estimated rate ratio was 0.664 (95% CrI 0.513, 0.860) (SC+IV data for mepolizumab). The median estimated rate ratio for hospitalisation was comparable to that for omalizumab 0.932 (95% CrI 0.350, 2.490). The analysis of the change from baseline in predicted FEV_1 indicated that mepolizumab and omalizumab again are broadly comparable. The point estimate was 0.645 (95% CrI -2.652, 3.959).

Safety profile

Overall, the safety profile of 100 mg SC was comparable to placebo. However, the incidence of local site reactions when administered as a SC dose was higher. Reassuringly, the overall rate of these reactions was low (8% for mepolizumab vs. 3% for placebo) and the events were generally mild, transient, managed with routine supportive care and did not generally result in discontinuation (a total of 2 events in both PCSA and OLE studies) of study medication. Mepolizumab has demonstrated low immunogenic potential (6%) and most anti-mepolizumab antibodies were transient, the majority occurring only after the first administered dose. Neutralising antibodies were detected in one subject. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients. In addition, other adverse events of special interest (i.e. hypersensitivity, malignancy, CV events, and infections) have not been associated with an increased risk following mepolizumab treatment from either the RCT Studies or with longer exposure as observed from the OLE Studies, COSMOS and COLUMBA. Anaphylaxis has not been associated with mepolizumab treatment. However, it should be noted that rare events, such as anaphylaxis, may not be detectable within the scope of a Phase III program and will continue to be monitored through post-marketing surveillance.

4.13.2 Discussion of strength and limitations of the clinical evidence base

4.13.2.1 Internal Validity of Studies

The results of the comparison with Standard of Care is based on high quality well designed Phase 3 studies comparing the interventions of interest in the relevant patient population and therefore have a high degree of internal validity.

Subgroup subject numbers

The results of the GSK proposed population is based on a post hoc analysis of the most relevant outcomes of the MENSA and SIRIUS studies. Whilst in the subgroup for more rare events (e.g. exacerbations requiring hospitalisation) patient numbers become too low to demonstrate statistical significance these results are consistent with those from the larger ITT population analysis. However this is not unexpected finding where subgroup analyses are performed in this way. Hemmings et al. states the following on p11 in his 2014 paper regarding appropriate regulatory review of subgroup analyses: “Next, the reviewer must expect to see the confidence interval for many subgroups cross the point of unity, corresponding to a nominally non-

significant statistical test, simply because of the reduced statistical power associated with the smaller sample size for each subgroup".[144]

Therefore, interpretation of the results of subgroup analysis should rather focus on the consistency of point estimates.

The entirety of the results from these subgroup analyses provide further support of the robustness and consistency of the treatment effect and convincing evidence that the identified more severe GSK proposed population, with an increase unmet need (≥4 exacerbations/year or dependency on OCS), had a additional clinical benefit from add-on treatment with mepolizumab compared to standard of care.

As discussed above the results in the proposed GSK population did not include the results from DREAM the dose ranging study. However a meta-analysis of the ITT results of MENSA and DREAM has been performed and supports the assumption that the results of MENSA would be broadly representative of the total trial population.

Comparison to Omalizumab

With the available evidence we have attempted to address the comparative efficacy of add-on mepolizumab versus omalizumab through a Bayesian NMA. Whilst it is not possible to provide evidence of the relative effectiveness of mepolizumab in the proposed GSK population compared to the NICE recommended population due to the lack of IPD for omalizumab, conclusions can still be drawn from a comparison between the ITT populations for both interventions of interest. Given the results in the ITT population it is a reasonable assumption that in the overlap population mepolizumab would be at least as effective as omalizumab.

In addition in a recent publication (Hanania et al., 2013, a post hoc analysis of the EXTRA study), patients with a higher level of eosinophils at baseline experienced a greater reduction in exacerbations on omalizumab. However it appears unlikely that a revision of the omalizumab efficacy estimates would be large enough to change the conclusions of the NMAs. We therefore still consider our analyses to be informative for this Decision Problem and conclude that that mepolizumab is at least as effective as omalizumab in the overlap population.

4.13.2.2 External validity of studies

Relevance of the GSK proposed population to the UK

The identified subgroup of patients from our clinical trial population that had additional benefit from add on mepolizumab therapy (GSK proposed population) was validated and supported clinically by independent severe asthma specialists in advisory boards.

Clinical specialists deemed the GSK proposed population representative of the UK severe refractory eosinophilic asthma population and readily identifiable by tertiary specialists in a severe asthma service setup. With respect to the specific criteria identified:

(a) Blood eosinophils are measured as part of a full blood count blood test, which is routine practice when assessing severe asthma patients. Thus, no additional resources, interventions for patients are required for this blood marker. Whilst during the regulatory review the EMA decided not to include any specific eosinophil levels in the indication statement this was reflective of the difficulty identifying a specific cut off point below which the efficacy could not be justified. However in a context of a review by NICE, where it is important to target a new intervention at those patients more likely to benefit in order to provide a cost effective use of NHS resources eosinophils remain an important and reliable predictor of enhanced effectiveness.

(b) The eligibility criterion of ≥4 exacerbations in the previous year or dependency on maintenance corticosteroid is already practiced by clinicians for omalizumab in severe allergic asthmatic patients (need [for] continuous or frequent treatment with oral corticosteroids, at least 4 courses in the last year).

The severe asthmatic population remain at high risk from acute exacerbations and persistent symptoms despite optimised standard of care. Therefore, a critical treatment goal in this population is the reduction of clinically relevant exacerbations and alleviation of symptoms. In addition this population has a high use of OCS which is accompanied by impactful untoward side effects and increased risk profile. An additional treatment objective therefore is to reduce exposure to OCS – particularly in those patients receiving maintenance OCS. The primary outcome measures of level of exacerbations and use of oral corticosteroids were pertinent to this patient population.

All patients in the clinical trials were optimised on standard of care, which included high dose inhaled corticosteroids (ICS) and additional maintenance treatment(s). This is in line with step 4 and 5 (when mOCS is added) of the BTS/SIGN guidelines and consistent with best evidence based clinical practice for the management of severe asthma patients in the UK, as well as consistent with current NICE guidance for omalizumab.

The RCTs were multi-national trials however a small number of UK patients were recruited in each case. It is not unexpected that participation of UK trial centres was limited given the small underlying population of severe refractory eosinophilic asthma patients relative to other asthma populations. In addition the studies were subject to competitive recruitment. Importantly however, there are no identified reasons, nor are there likely to be any unidentified reasons, why any geographical differences would render the results of these studies inapplicable in England and Wales. The demographic and disease characteristics of participant patients in the trials are similar to those described in other Phase III studies of severe asthma, and are representative of patients at stage 4 and stage 5 of the BTS/SIGN treatment algorithm.

In summary, there are no reasons to believe that the clinical benefits of mepolizumab seen in severe asthma studies would not be applicable to the patients eligible to receive this treatment in UK clinical practice.

Relevance of Outcomes Measures to clinical benefits for patients

The GSK proposed population analysis examined the most relevant endpoint for the decision problem: rate of clinically significant exacerbations, ED visits and/or hospitalisations; asthma control (ACQ); quality of life (SGRQ); OCS dose reduction while maintaining asthma control.

Patients on maintenance OCS experience an additional clinical benefit from a reduction in OCS use. In the total ITT population of SIRIUS 48% of patients were exposed to OCS for more than 5 years. It is also noteworthy that in MENSA, approximately a quarter (23 to 27%) of patients were receiving daily OCS and the mean average dose of prednisolone was 13.2 mg. Thus there is a clear unmet need to reduce the dose and dependency on OCS in patients with severe asthma.

Add-on mepolizumab therapy's potential to reduce maintenance OCS dosing while maintaining asthma control was supported in SIRIUS. Patients on maintenance OCS are at risk of significant side effects, a risk often accepted as a trade off to achieve reduced asthma exacerbation rates. Only a number of patients matched the GSK proposed population subgroup selected from the ITT population in SIRIUS. The reduced number of subjects looked at in the subgroup meant that while there was a comparable trend in reduction of OCS dose in the GSK proposed population vs. the ITT population statistical analysis was inadequately powered to reach a robust conclusion. However, subjects in the GSK proposed population represented the majority of patients that experienced a reduction in OCS dose observed in the ITT population (see above). Thus, it can be concluded that the GSK proposed population identified those patients that experienced an increased benefit from add-on mepolizumab therapy.

In the GSK proposed population excluding mOCS users with < 4 exacerbations in MENSA, the rate of clinically significant exacerbations improves by 61% in subjects with ≥150cells/µl baseline blood eosinophils and ≥4 Exacerbations in past year. When the population is extended to include subjects on baseline maintenance OCS (the GSK proposed population, with ≥150 cells/µl baseline blood eosinophils and ≥4 exacerbations in past year or dependency on maintenance OCS use) this is reduced to 50%. Despite their significant side effects, OCS has a therapeutic benefit in terms of asthma control. This explains the lessened benefit observed with add-on mepolizumab therapy in maintenance OCS users. However, the additional benefit in reducing systemic corticosteroid exposure, associated with significant side effects, is not reflected by these results and indeed difficult to capture in clinical trials. This needs to be taken into consideration when evaluating the results of the GSK proposed population, where some of the benefits may be masked by mOCS.

Quality of life measure

Both the EQ-5D and Asthma Quality of Life Questionnaire (AQLQ) where used in the phase IIb DREAM study. Neither were sensitive and specific enough to discriminate between differences in severity at baseline in the severe asthma patient population studied. Specifically for EQ-5D 30% of patients reported full quality of life at baseline despite the severity of the disease in this patient population, Thus, a more specific quality of life measurement, SGRQ validated for asthma was chosen in the phase III studies, SIRIUS and MENSA (please see section 4.7.4 for GSK proposed population results and 4.7.5 for a more in depth discussion on quality of life measure). Overall, evidence supports the SGRQ as having content validity, construct validity, and

responsiveness in patients with severe asthma. Based on the utility of this tool in patients with severe asthma, the SGRQ was introduced as the quality of life instrument for the Phase III studies MENSA and SIRIUS. SGRQ total and domain scores have been shown to strongly correlate to the ACQ;[132] an outcome measure in the phase III trials that showed the same clinically and statistically significant improvement for mepolizumab add-on therapy over standard of care.

Long-term efficacy of mepolizumab therapy

In addition to the double blind studies supporting this patients had the opportunity to continue treatment as part of open label extension studies. These demonstrated that the benefits could be observed for an additional year, albeit that these extensions studies were open label. The draft SPC by the EMA states 'the need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations'. In the clinical trial program none of the outcomes measures were found to be predictive of a future response to mepolizumab therapy. In current clinical practice patients are reviewed on a regular basis by physician (2-4 times per year) and nurses (at administration appointments). Thus, a holistic patient assessment of treatment goals (i.e. exacerbation reduction, OCS dose reduction, quality of life, asthma control, etc) at those review time points, evaluating risk/benefit of mepolizumab therapy for each individual patient, seems clinically most appropriate. In the extension studies a formal review of this nature was not required in the protocol and whether to continue was left to the investigators opinion. Given that this was a clinical trial setting and patients would have no opportunity to access mepolizumab outside of a clinical trial setting it is possible that the withdrawal rates observed in these extension studies would be less than that might be experienced in clinical practice.

Mortality in severe asthma

There were nine deaths in the mepolizumab trial program (none related to the therapy) and even fewer were related to asthma (3). The study lengths ranged from 24 to 52 weeks in the RCTs (additional 52 week OLE of MENSA and SIRIUS), and arguably were insufficiently powered to assess mortality in asthma as an outcome measure, even in this severe asthma population. Longer-term studies would be more appropriate to investigate any effect of mepolizumab on asthma death. However NRAD reported that 39% of UK asthma deaths were among severe asthma patients suggesting that mortality remains an important outcome. Furthermore, the majority of asthma death occurred outside hospital and emergency department settings. Indeed, there were only small numbers of patients attending emergency department visits and/or hospitalisations in each individual study, and hence even smaller numbers of patients were identified in the GSK proposed population. Nevertheless, a numerical reduction in emergency department visits and/or hospitalisations could be observed.

Indeed, any reduction in exacerbations is a major benefit to patients and health care services; in addition to being associated with considerable morbidity and mortality, exacerbations associated with hospitalisation are the severest form of these events, and have been linked to a long term risk of accelerated lung function decline.[118-120] In one study, in which patients were followed for an average of 2 years, the mortality

rate was 6.7 per 100 patient-years, with a higher severity of asthma associated with higher risk.[145] One of the strongest predictors of death due to asthma is asthma-related hospitalization (including hospitalization as a result of an exacerbation).[31,32] A meta-analysis found that a history of hospital and/or intensive care unit admissions significantly increased the odds of a near fatal or fatal asthma event, with an odds ratio of 2.62 (p=0.04) for hospital and 5.14 (p=0.001) for intensive care unit admissions.[146] Any treatment which can reduce hospitalisations in patients at high risk is an important development in an area of currently unmet medical need.

Therefore whilst it is not possible to demonstrate a benefit in mortality from mepolizumab therapy from the clinical trial programme it is not an un-reasonable assumption that the impact on reducing exacerbations and patient dependence on systemic corticosteroids whilst maintaining asthma control may have a longer term benefit on patients mortality.

4.14 Ongoing studies

A list of ongoing studies is shown in Table 95.

Table 95 List of ongoing studies

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.
COLUMBA	SC Mepolizumab 100mg	DREAM (MEA112997) population. Study Participation: Received at least 2 doses of double-blind investigational product during the MEA112997 trial.	A Multi-centre, Open-label, Long Term Safety Study of Mepolizumab in Asthmatic Subjects Who Participated in the MEA112997 Trial. Anticipated completion April 2018.	NCT01691859 https://clinicaltrials.gov/ct2/show/NCT01691859?term=Mepolizumab&rank=15
MUSCA	SC Mepolizumab 100mg	≥12 years of age, severe refractory eosinophilic asthma patients (high dose ICS + additional controllers, ≥2 exacerbation in last 12 months, blood eosinophil inclusion criteria)	A Phase 3, multi-centre, placebo-controlled, double-blind, parallel-group study to evaluate the efficacy and safety of mepolizumab adjunctive therapy in participants with severe eosinophilic asthma on quality of life and additional markers of asthma control. The overall intent of the current study is to more fully explore the impact of mepolizumab on health-related quality of life (HRQL) and other measures of asthma control, including lung function, anticipated completion 2016.	NCT02281318 https://clinicaltrials.gov/ct2/show/NCT02281318
IDEAL Study completed and now at analysis stage for final report by end of November/beginning of December	No drug intervention	≥12 years of age, severe asthma patients (high dose ICS + additional controllers)	Cross-sectional study for Identification and description of severe asthma patients: aims to estimate the potential overlap of patients eligible for treatment with mepolizumab and those eligible for treatment with omalizumab, anticipated completion Q4 2015.	NCT02293265 https://clinicaltrials.gov/ct2/show/NCT02293265

PK/PD study in Children	SC Mepolizumab 40mg SC Mepolizumab 100mg	6 to 11 years of age, severe asthma patients (high dose ICS + additional controller, ≥2 exacerbation in last 12 months) with eosinophilic airway inflammation; elevated peripheral blood eosinophil count of >=300 cells per microlitre (cells/μL) demonstrated in the past 12 months or elevated peripheral blood eosinophil count of >=150/μL at visit 1.	An Open-label Study to Characterize the Pharmacokinetics and Pharmacodynamics of Mepolizumab Administered Subcutaneously in Children From 6 to 11 Years of Age With Severe Eosinophilic Asthma	NCT02377427 https://clinicaltrials.gov/ct2/show/NCT02377427?term=mepolizumab&rank=1

5 Cost effectiveness

Overview
A Markov cohort model was developed to assess the cost-effectiveness of add-on mepolizumab to standard of care (SoC) alone and add-on omalizumab (in the overlap population; see Section 3.3) from the perspective of NHS England and Wales (refer to the Decision Problem in Section 1). The GSK proposed population for which we seek guidance is as follows:

- **Severe refractory eosinophilic asthma in adults with a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or dependency on systemic corticosteroids (maintenance oral corticosteroids [mOCS]).**

This is referred to as the '*GSK proposed population'.*
Section 5 will focus on the cost-effectiveness for this targeted population. The cost-effectiveness of the ITT population (based on the inclusion criteria of MENSA) is presented for completeness in section 5.7 and associated sensitivity analyses are provided in Appendix 8.17.

Continuation criteria are applied for add-on mepolizumab at 12 months based on exacerbation reduction (see section 5.2.4), and as recommended in the draft SmPC. A summary of populations presented is provided in Table 99.

5.1 Published cost-effectiveness studies

5.1.1 Identification of studies

A systematic literature review was undertaken to identify cost-effectiveness studies relevant to the Decision Problem. The eligibility criteria implemented is provided in Table 96 and search strategy details are provided in Appendix 8.9. The search was undertaken on 28th July 2015 (an update to original searches conducted on 5th August 2014). The search was undertaken according to NICE requirements.[147]

Table 96 Eligibility criteria used in the search strategy

Dimension	Inclusion criteria	Exclusion criteria
Disease and treatment	Severe asthma*	• Other diseases • Asthma of other levels of severity
Patient group	Adults and children (≥12 years of age)**	Children of < 12 years of age
Article type	Original cost-effectiveness analysis of the "mabs" and all maintenance OCS	• Review articles in which cost-effectiveness is not the major focus • Letters or editorials that comment on results of an economic evaluation published elsewhere.
Publication time	Without restriction	NA
Publication language	Without restriction – all	No exclusion due to language

	languages	

*Protocol deviation was decided upon by also including studies with moderate-to-severe asthma; severe asthma alone retrieved fewer results and therefore deemed too limiting.
**The original searches were conducted prior to the regulatory process and therefore the age inclusion reflected the trial inclusion criteria. This was not altered at a later date to reflect the regulatory application. Studies still deemed relevant for informing model structural parameters.

5.1.2 Description of identified studies

Out of 3726 unique records, 15 cost-effectiveness studies were deemed eligible for inclusion (see Table 96).[148-162] The detailed search and selection process and PRISMA flow chart is provided in appendix 8.9. No studies identified captured the cost effectiveness of mepolizumab compared with SoC alone. Two studies reported the cost-effectiveness of treatments in moderate-to-severe asthma but were not considered relevant. One abstract (Bogart, 2015[161]) reported the cost-effectiveness of refractory asthma treatment strategies from a US perspective although the interventions and comparators were not clear. The abstract did report the cost-effectiveness of mepolizumab without bronchial thermoplasty, however this is not deemed relevant to this appraisal; bronchial thermoplasty was not identified as a comparator of interest (see Section 3). One study reported the cost-effectiveness of tiotropium versus SoC in a poorly controlled asthma population.[163] Tiotropium has not been identified as a key comparator in this appraisal and therefore is not discussed further. Please refer to the systematic literature review of economic evidence provided in the reference pack.[164]

The remaining 13 studies reported the cost-effectiveness of omalizumab compared with SoC / Usual care. Omalizumab is a comparator in this appraisal in an overlap population of severe asthma patients expressing both allergic and eosinophilic phenotypes. The 15 studies are outlined in Table 97. Two of the 13 omalizumab studies are considered relevant to this appraisal given the patient population, perspective and country of study (Norman 2013 and Faria 2014).[152,159]

Norman (2013) summarises the NICE Assessment Group's approach to evaluating the (clinical and) cost-effectiveness of omalizumab which formed part of the NICE multiple technology appraisal (MTA) (TA 278) in patients with severe persistent allergic asthma. A quality assessment is provided in appendix 8.10.

Norman et al[152] developed a 5-state model with states of day-to-day asthma symptoms (which included non-clinically significant exacerbations (morning, night time and day time symptoms), a clinically significant non-severe exacerbation (PEF or FEV_1 greater than 60% of personal best), a clinically significant severe exacerbation (PEF or FEV_1 lower than 60% of personal best), asthma related death and death from all causes. The model assessed costs and outcomes over a lifetime horizon from an England and Wales NHS perspective and assumed responders to omalizumab treatment remained on treatment for 10 years.[152]

The baseline rate of exacerbations, proportion of responders to omalizumab treatment and the effect of omalizumab on exacerbation frequency were derived from a Phase 3 study INNOVATE[58] for adults and adolescents ≥ 12 years. Note that the MTA also considered people aged 6-12 years. All cause mortality and asthma related mortality (compared with people without asthma) were included as part of the

natural history of the patient cohort.[152] Resource used was obtained from the trial data and costed using NHS reference costs and Personal Social Services Research Unit reported costs (PSSRU). Day-to-day quality of life was based on EQ-5D data collected from EXALT[74], an international multicenter, randomised, open label, parallel-group study. The decrement in utility associated with an exacerbation, and duration of the utility decrement was derived from a UK-based 4 week prospective study.[165] Adverse events were not considered in the base case analysis. A scenario analysis explored the impact of OCS related side effects in people on maintenance OCS. Relative risks of an event due to maintenance OCS were obtained from the literature, utility decrement was obtained from a WHO burden study[166] and applied in such a way that DALYs were deemed equivalent to QALYs and aggregate costs were taken from the average annual cost of each outcome.[152] Three populations were evaluated: the overall population, only those hospitalised 12 months prior to trial entry and only those on maintenance OCS at trial entry. The base case ICER was £83,822 for omalizumab compared with SoC. A summary of the reported basecase ICERs with incremental costs and QALYs is provided in Table 98. The Assessment Group concluded that the key drivers of the cost-effectiveness of add-on omalizumab versus SoC alone were assumed asthma-related mortality rates, the extent of improvement in HRQL of omalizumab treated patients, and OCS related adverse events.

Table 97 Summary of the 15 economic evaluations identified from the systematic literature review.

Reference	Model	Intervention	Population	Outcome	Summary results
1. Oba and Salzman 2004[148] US (Third-party payer)	Cost-effectiveness analysis Used individual patient level data	Usual care: ICSs plus rescue medication	Adolescents (≥12 years) and adults with moderate-to-severe allergic asthma, uncontrolled despite ICSs, average age of 39 years, 54% female)	Cost per 0.5-point increase in the AQLQ score	$ 378 per 0.5-point AQLQ increase
				Cost per successfully controlled day (SCD)	$ 525 / SCD
2. Dewilde et al. 2006[153] Sweden (societal)	Cost-utility 5-state Markov model	Optimized Standard therapy at GINA step 4: high dose ICS plus LABA and additional rescue medication	Severe persistent asthma patients, average age of 43 years, 68% female Response to omalizumab was assessed at 16 weeks and it was assumed that non-responders reverted back to standard therapy	ICER	ICER = € 56,091/ QALY gained
3. Brown et al. 2007[154] Canada	Cost-utility 5-state Markov model	Standard therapy (high-dose ICS plus LABA and additional controller medication if required)	Canada (health-care payer) Patients with severe persistent allergic asthma despite high-dose ICS plus LABA	ICER	ICER = € 31,209/ QALY gained
4. Wu et al. 2007[155] USA	Cost-effectiveness and cost-utility analyses 3-state Markov model	ICSs with quick relievers alone	US (societal) Adult patients with severe uncontrolled asthma	ICER	ICER = $ 821,000/ QALY gained
				Cost per Symptom-free day (SFD)	$120 per SFD gained
5. Campbell et al. 2010[156] USA	Cost-utility 6-state Markov model	Standard therapy : ICS plus rescue and additional medication as required	US (US payer) Patients with moderate to severe persistent asthma, uncontrolled with ICSs, average age of 40 years, 60% female Response to omalizumab was assessed at 16 weeks and it was assumed that non-responders reverted back to standard therapy	ICER for base-case (and responders subgroup)	ICER= $ 287,200/ QALY gained ($ 172,300 / QALY gained)
6. Dal Negro et al. 2011[149] Italy	Cost-utility	Optimized standard therapy: high-dose ICS and LABAs (GINA 2014 step 4)	Italy (health-care payer) Patients sensitised to perennial antigens with severe difficult to treat asthma, who have been using omalizumab in addition to optimised therapy Response to omalizumab was assessed at 16 weeks and it was assumed that non-responders reverted back to standard therapy	ICER	ICER= € 26,000/ QALY gained
				Cost per month with one FEV_1 predicted percentage point gained	€ 21.9 / %FEV_1
				Cost per month with one Asthma Control Test (ACT) point gained	€ 57.3/ ACT point gained

7. Dal Negro et al. 2012[150] Italy	Cost-utility	Standard therapy: Chronic high-dose antiasthma treatments including LABAs, OCS, Anti-LTs , antibiotics , SABAs, parenteral CS, xanthines	Italy (health-care payer) Patients (≥12 years) with severe, persistent atopic asthma. Average age of 45.4 years. 50% female.	ICER	ICER = € 23,880/ QALY gained
8. Morishima et al. 2013[157] Japan	Cost-utility 4-state Markov model	Placebo plus standard therapy: high-dose ICS, LABA, theophylline, and leukotriene antagonists	Japan (societal) Patients (20-75 years old) with moderate to severe asthma. Average age 50 years. 50% women. Response to omalizumab was assessed at 16 weeks and it was assumed that non-responders reverted back to standard therapy	ICER (and responders subgroup)	ICER = US$ 755,200/ QALY gained (US$590,100 / QALY gained)
9. Levy et al. 2014[151] Spain	Cost-effectiveness and cost-utility analyses	Standard therapy	Spain (National Health System) Patients (>14 years) with uncontrolled severe persistent asthma. Average age 54. 70.2% women	ICER	ICER = € 26,864.89/ QALY gained
				Cost per exacerbation avoided	€ 462.08 per exacerbation avoided
10. Sonathi et al. 2014[160] Greece (societal)	Cost-utility analyses	Adult patients with severe allergic asthma.	Omalizumab vs. Standard therapy: primarily comprised ICS, LABA and SABA	ICER	Based on INNOVATE trial data ICER= € 27,888/ QALY gained Based on the RWE from a prospective observational study conducted in Greece ICER = € 27,255/ QALY gained
11. Suzuki et al. 2015[162] Brazil (private health-care system)	Cost-effectiveness	Uncontrolled severe allergic asthma.	Omalizumab vs. Standard of care	Incremental cost per clinically significant exacerbation (CSE) avoided	BRL 9,289/CSE avoided
				Incremental cost per clinically significant severe exacerbation (CSSE) avoided	BRL 17,597/CSSE avoided
12. Willson et al. 2014[158] UK (National Health System)	Cost-utility analyses	Asthma patients who were poorly controlled, confirmed by an Asthma Control Questionnaire 7 (ACQ-7) score of 1.5 or greater despite usual care comprising at least a high-dose ICS/LABA. Average age	Tiotropium vs. Usual care (high-dose ICS/LABA)	ICER	ICER = £21,906/QALY gained

		53.*			
13. Bogart et al. 2015[161] US (health-care payer)	Cost-utility analyses	Adult with severe refractory asthma.	Intervention and comparators are not explicitly reported in the abstract provided	ICER	Mepolizumab without bronchial thermoplasty was the most cost-effective option for biologics responders ICER = $ 21,388/ QALY gained Among patients who do not respond to biologic treatment, bronchial thermoplasty is a cost effective treatment option ICER = $ 33,161/ QALY gained
14. Norman et al. 2013[152] UK	Cost-utility analyses	Adults and adolescents (≥12 years old) with severe uncontrolled asthma	Omalizumab versus standard therapy Step 4 (high dose ICS and LABA) and Step 5 (frequent or continuous OCS treatment)	ICER	£83,822/QALY gained
				Hospitalisation sub-group; those hospitalised 12 months prior to trial entry	£46,431/QALY gained
				Maintenance OCS subgroup	£50,181/QALY gained
15. Faria et al. 2014 UK	Cost-utility analyses	Severe persistent allergic asthma patients (≥12 years) uncontrolled at Step 4 and in the process of moving up to Step 5 and patients controlled at Step 5 whose asthma would be uncontrolled if they were on Step 4 therapy	Omalizumab versus standard of care; optimised therapy at step 4 or 5		

(*)Both treatment arms included an 'early response phase' transition matrix reflecting weekly transition probabilities across the first 8 weeks of the trial duration and was applied for the first eight cycles of the cost-effectiveness model. A 'late response phase' transition matrix reflecting weekly transition probabilities across the remaining 40 weeks of the clinical trial duration was also included in the cost-effectiveness model for both treatment arms. The 'late response phase' transition matrix was applied from the ninth cycle of the cost-effectiveness model and was used to extrapolate effectiveness over the remainder of the time horizon.

XX Considered relevant and discussed further in the main body of the submission; see section 5.1.2

Table 98 Summary of the cost-effectiveness results for add-on omalizumab versus SoC alone.[152]

Add-on omalizumab versus Soc alone	∆ £	∆ QALYs	ICER Adults and adolescents only
Overall population			
Base Case	**£39,720**	**0.47**	**£83,822**
Asthma related mortality from Watson et al., 2007[167]	£40,260	0.87	£46,029
EQ-5D mapped from AQLQ collected in INNOVATE[58]	£39,728	0.77	£52,236
Hospitalised 12 months prior to study entry			
Base Case	**£39,377**	**0.85**	**£46,431**
Asthma related mortality from Watson et al., 2007[167]	£39,896	1.26	£31,576
EQ-5D mapped from AQLQ collected in INNOVATE[58]	£39409	0.89	£44,430
On maintenance OCS at study entry			
Base Case	**£33,093**	**0.66**	**£50,181**
Asthma related mortality from Watson et al., 2007[167]	£33,758	1.13	£29,657
EQ-5D mapped from AQLQ collected in INNOVATE[58]	£33154	0.56	£50,068

During the appraisal process, the NICE Appraisal Committee asked for analyses in three additional populations[137]:

1) people with severe persistent allergic asthma, maintained on OCS and who were hospitalised in the year before
2) people with severe persistent allergic asthma, maintained on OCS but who have not necessarily been hospitalised in the year before treatment
3) people with severe persistent allergic asthma who are on maintenance or frequent course of OCS (≥4 courses in the previous year) but who have not necessarily been hospitalised in the year before treatment.

The Assessment Group was also asked to model alternative assumptions on mortality rates, rates of clinically significant exacerbations for very severe asthma, treatment duration, adverse effects of OCS and carer benefits.

The resultant base case ICERs across the 3 additional populations (for adults, adolescents and children) were £33,077, £33,150 and £32,229/QALY gained respectively. Further scenario and threshold analyses were conducted. With a patient access scheme (PAS) approved this brought the ICER to £23,200/QALY gained for a combined population (children, adolescents and adults) on maintenance or frequent courses of OCS in the year before receiving omalizumab. The Committee was persuaded that the uncaptured benefits of reducing the dependence on OCS was sufficient to justify the ICER.[137] As a result omalizumab was recommended by NICE in 2013, as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people ≥6 years who need continuous or frequent treatment with OCS (defined as ≥4 courses in the previous year), alongside an agreed PAS.[137] We consider the discussion described in the FAD[137] that ensued between the manufacturer, the

Assessment Group and the NICE committee to be of relevance in the consideration of the approach to the modelling in this appraisal, namely:

- Assumptions on asthma related mortality; asthma-related mortality rate mid-point between two published sources (Watson 2007[167] and de Vries 2010[168]) plus 15%.
- The degree of improvement in quality of life as a result of being on biologic therapy.
- The impact of long term OCS on costs and outcomes.

The most recent publication, Faria 2014[159] reports an independent cost-effectiveness assessment of omalizumab building on the previous NICE assessment and addresses key areas of uncertainty. Incorporation of the adverse effects from OCS had little impact on the ICER; estimates of QALY burden were small (~0.023 QALYs lost), additional costs were considered a likely underestimate (£205.60/ year) and QALY losses and costs were only applied after omalizumab treatment discontinuation. With regards the effect of asthma related mortality, the risk required to achieve an ICER below £30,000/QALY gained was lower in the more severe sub-groups. The analyses concluded that with the agreed PAS omalizumab needs to be carefully targeted to ensure value for money.

5.2 De novo analysis

5.2.1 Patient population

The economic evaluation addresses the Decision Problem (Section 1) and seeks to explore the cost-effectiveness of add-on mepolizumab compared with SoC alone (or versus add-on omalizumab in the overlap population) in adults with severe refractory eosinophilic asthma. These people are considered optimised on therapy at Step 4 and 5 of the BTS/SIGN guidelines,[22] on high dose ICS and additional maintenance treatment[s]. As a cohort it should be noted that a proportion of people at Step 5 will be on maintenance OCS (see Table 99).

Add-on mepolizumab showed enhanced clinical benefit in sub-populations of the anticipated licensed indication (see Section 4.7). This was demonstrated in patient populations with a persistent blood eosinophil count of ≥150 cells/μL at initiation of treatment and ≥4 exacerbations in the previous year. Mepolizumab also demonstrated the reduction of maintenance OCS dose which is desirable because of the adverse events associated with both short and long-term use. Mindful of today's NHS environment with limited resources and in the context of the current guidance for add-on omalizumab for severe persistent allergic asthma we seek guidance for mepolizumab from the Committee as an option for:

Severe refractory eosinophilic asthma in adults (≥18 yrs) with a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or are dependent on mOCS (GSK proposed population)

The cost-effectiveness of add on mepolizumab will be presented for the following populations shown in Table 99. Comparisons with add-on omalizumab in the overlap population will only be made in the full ITT population. Due to the limitations

of the available evidence for omalizumab it was not possible to perform comparisons with restricted populations through a network meta-analysis (see section 4.10).

Table 99 Summary of the patient populations evaluated and presented in the de novo analysis

Population (BTS/SIGN treatment Step)	Add-on mepolizumab vs. *In severe refractory eosinophilic asthma patients (≥18 years) on high dose ICS and additional maintenance treatment[s])*	SoC alone	Add-on omalizumab
4/5 (greater proportion of Step 5)*	**GSK proposed population [population for which GSK seeks guidance]** *Patients who have a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or dependency on maintenance OCS* • Represents approximately of [redacted] of the MENSA population ([redacted]).	✓	-
4/5*	**GSK proposed population excluding mOCS users with <4 exacerbations in the previous year** *Patients have a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year* • Represents approximately [redacted] of the MENSA population ([redacted])). In this population, mepolizumab appears to be more cost-effective compared with the GSK proposed population. Patients on maintenance OCS are likely to be more controlled; however the economic evaluation does not adequately capture the long- term costs and consequences of being on maintenance OCS.	✓	-
4/5	**ITT Population (defined by the inclusion criteria of MENSA)** Patients have a blood eosinophil count ≥150 cells/μL at initiation of treatment or a blood eosinophil count ≥300 cells/μL in the prior 12 months, who experience ≥2 exacerbations in the previous year • Base case results will be presented in section 5.7. • Sensitivity analyses will be presented in Appendix 8.17	✓	✓ *Based on NMA on full trial population*

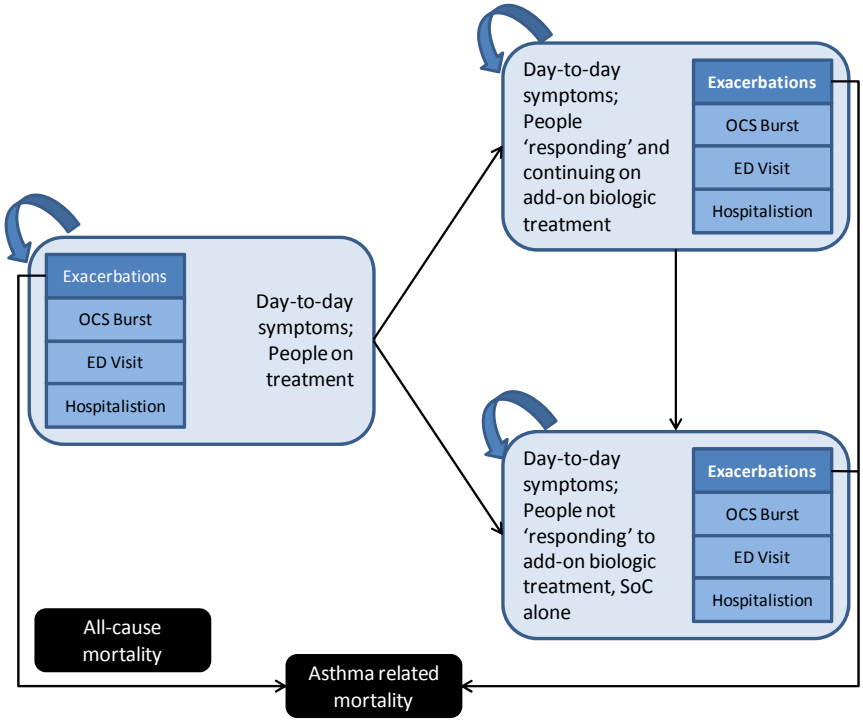
**Note that the long term costs and consequences will only be considered as part of a scenario analysis.*

5.2.2 Model structure

Asthma is a chronic heterogeneous lung disease characterised by inflammation, narrowing of the airways, and reversible airway obstruction (see section 3). The majority of people with asthma live a full and active life.[28] However, for a small proportion – around 5%, symptoms are more severe and patients experience uncontrolled asthma despite attempts to control their disease following step-wise treatment recommendations (e.g. high dose ICS plus additional maintenance treatment[s]).[20] This group of severe refractory asthma patients suffer from frequent exacerbations, limited control of symptoms, and compromised quality of life.[20] Patients with severe asthma are considered very differently from the majority of asthmatics.[17] They require systematic assessment[169] and receive care in specialist centres. Severe asthma can be further split into phenotypes and one specific type is eosinophilic asthma, which mepolizumab targets (severe refractory eosinophilic asthma, refer to Section 2.1). In order to capture the day-to-day quality of life of

severe refractory eosinophilic asthma patients, a cohort Markov model was developed (see Figure 26) in MS Excel 2013 as follows:

Figure 26 Schematic of the Markov model structure



OCS oral corticosteroid; ED emergency department; SoC Standard of care

Patients enter the model with the diagnosis of severe refractory eosinophilic asthma despite best SoC (high dose ICS and additional maintenance treatment[s]. The model consists of three key health states which define day-to-day symptoms for patients on an add-on biologic pre-continuation assessment and post-continuation assessment (responders and non-responders). Patients start in health state 'Day-to-day symptoms; people on treatment' which captures the day-to-day quality of life associated with the treatment in question and includes the occurrence of symptom-free periods as well as non-clinically significant exacerbations (morning, night-time and day-time symptoms). This reflects the day-to-day quality of life of living with severe asthma.

In subsequent model cycles (4-weekly) patients remain in health state up until the point of continuation assessment. This is relevant for patients on biologic treatment. For mepolizumab the continuation review is applied at 12 months (see section 5.2.4; the subset of patients meeting the continuation criteria was isolated from MENSA and post-hoc data analyses informed their corresponding exacerbation rate and health status). For omalizumab the stopping rule is applied at 16 weeks (see section 5.2.4; information taken from NICE TA 278[137] and Phase 3 INNOVATE[58]). This reflects the requirements of the SmPC for both interventions and good clinical practice, where patients who do not experience the expected benefit should not be continued on biologic treatment. Patients not meeting the continuation criteria are assumed to discontinue biologic treatment and return to SoC alone with corresponding exacerbation rates and health status; no residual biologic treatment effects are assumed. The model also allows for a transition to SoC alone due to

biologic treatment withdrawal (natural attrition rate). Likewise, discontinuers are assigned to exacerbation rates and health status based on the SoC arm, similar to patients not meeting the continuation criteria. People not initiated on biologic treatment continue on SoC alone for the duration of the model.

Whilst remaining in 'state' patients can experience a clinically significant exacerbation event, defined in MENSA[16] as a "*worsening of asthma such that the treating physician elected to administer systemic glucocorticoids for at least 3 days or the patient visited an emergency department or was hospitalised*". Exacerbations are not treated as a health state, but observed as a transient event which occurs within an asthma symptom health state. During each cycle patients may experience one of the three types of clinically significant exacerbations: an exacerbation requiring treatment with OCS, an exacerbation requiring an Emergency Department visit (ED visit), or an exacerbation requiring hospitalisation. The distribution of the type of exacerbation event is taken from MENSA (see Section 5.3). The rate of clinically significant exacerbations is dependent upon the therapy a patient is receiving, and for mepolizumab is taken from MENSA (see Section 5.3). The impact of each type of exacerbation is implemented by applying a utility decrement and a cost to treat the exacerbation.

There are 2 absorbing states; asthma related death and all-cause mortality (see Section 5.3.6). The risk of an asthma-related death is applied to all people experiencing an exacerbation. This is subject to a number of scenario analyses.

Lastly, the steroid-sparing potential of mepolizumab is considered in a separate scenario analysis by examining the safety and economic consequences of long-term OCS use.

The Markov model cycle length is 4 weeks, in line with the dosing schedule for mepolizumab. The relative short cycle length avoids the need for applying a half cycle correction. The model estimates the cost-effectiveness of mepolizumab over a life-time horizon, as asthma is a chronic, incurable disease. Biologic add-on therapy continues for a maximum of 10 years; afterwards patients continue on SoC alone. A treatment duration of 10 years was chosen which is consistent with the NICE MTA (TA 278) for omalizumab[152] and considered appropriate by our clinical advisors. No residual treatment effect of mepolizumab and the other biologic is assumed, and the clinical effects and health status of SoC patients immediately applies. Thus, after 10 years of treatment there are no differences in effects in the biologic treatment arm and the SoC arm. A summary of the features of the economic evaluation and justification for chosen values is provided in Table 100.

Table 100 Features of the economic analysis

Feature	Chosen value	Justification
Time horizon	Life time; patients enter the model with a mean age of 50.1 years.	Asthma is a chronic disease,[22] a life time horizon enables (differential) life time costs and outcomes to be adequately captured.[147] The mean age reflects the population recruited to MENSA which also represents late onset severe asthma patient population.

Cycle length	4 weeks	Reflects the four weekly treatment interval for mepolizumab
Half cycle correction rule	None	The cycle length is short
Measurement of health effects	QALYs	Consistent with Reference case[147]
Treatment duration of biologic therapy	10 years	Consistent with NICE appraisal of omalizumab[170] and agreed by clinical advisers.
Continuation criteria	Mepolizumab: 12 months based on level of control of exacerbations Omalizumab: 16 weeks post commencement of therapy based on overall asthma control.	Consistent with mepolizumab draft SmPC[15] Omalizumab SmPC[138], Norman 2013[152]
Discount rate assumed for utilities and costs	3.5%	Consistent with Reference case[147]
Perspective	NHS PSS perspective is considered qualitatively in section 5.5.4.	Reference case[147]

5.2.3 Intervention technology and comparators

Intervention: Mepolizumab
Add-on mepolizumab is a 100mg 4-weekly subcutaneous (SC) injection, for severe refractory eosinophilic asthma adult patients (≥18 years), already on high dose ICS and additional maintenance treatments(s). We seek guidance for a sub-population of the marketing authorisation for patients who have a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or are dependent on maintenance OCS (see the Decision Problem in Section 1). This represents approximately of [redacted] of the MENSA population ([redacted]), the source of most of the model parameters for mepolizumab (other than EQ-5D which is taken from DREAM).

Comparator 1: SoC alone
SoC alone represents the key comparator in this appraisal and is derived from the SoC arm of MENSA (other than EQ-5D which is taken from DREAM). Patients are on high dose ICS and an additional maintenance treatment(s) (such as LABA, leukotriene receptor antagonist or theophylline). Clinician feedback from 2 advisory boards considered the SoC arm to fairly reflect SoC in clinical practice and those treatments outlined in the BTS/SIGN guidelines.[22] These patients have limited alternative treatment options beyond maintenance OCS at Step 5.

Comparator 2: Add-on omalizumab
Omalizumab is considered a minor comparator in this appraisal. An initial sub-analysis of IDEAL (see Section 4.14), a non-drug interventional cross-sectional study undertaken to describe the severe asthma landscape and eligibility for biologic treatment, was conducted. This estimated that of those patients eligible for add-on mepolizumab in the GSK proposed population approximately [redacted] would also be eligible for omalizumab (in accordance with the omalizumab licence and NICE guidance (TA278).

Omalizumab (Xolair) is a humanised monoclonal anti-IgE antibody indicated in adults and adolescents (≥12 years) as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV_1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose ICS, plus a LABA.[138] Note that omalizumab is also recommended for children aged ≥6 - <12 years however, mepolizumab is not seeking a licence in children at this time and therefore this remains outside of the scope for this appraisal. Dose and dosing frequency of omalizumab varies patient-by-patient and is determined by the use of dosing tables based on a patient's body weight and IgE level. It is available as a pre-filled syringe (PFS) and administered subcutaneously every 2 or 4 weeks.[138]

NICE recommends omalizumab in a sub-population of the licensed indication (TA 278):

"Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older:

- *who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year),* ***and***
- *only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme.*

Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta$_2$ agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate."

To be clear, no person would receive both biologic treatments concurrently.

5.2.4 Review for continuation and stopping rules

Mepolizumab
It is anticipated that the SmPC for mepolizumab will convey that "*the need for continued therapy should be considered at least on an annual basis as determined by physician assessment on the patient's disease severity and level of control of exacerbations."* Exacerbation reduction is a key treatment objective for mepolizumab and as exacerbations are relatively infrequent events, and to avoid seasonal variability, an annual assessment was considered clinically relevant for mepolizumab. Therefore, in the model, at 12 months a continuation review is applied and those patients that see a worsening in exacerbation frequency from baseline are discontinued on mepolizumab, and receive SoC alone with its associated costs and outcomes.

This continuation review takes into consideration those patients at Step 5 on maintenance OCS, who may be less likely to experience a further reduction in exacerbations given their maintenance OCS therapy. However in these instances mepolizumab provides the opportunity to reduce OCS exposure and therefore the

longer term risks associated with OCS whilst maintaining asthma control. Table 104 summarises the proportion of patients discontinued on therapy which is derived from MENSA.

Clinician feedback suggests that this assessment can easily be incorporated into current clinical practice at one of the routine follow-up attendances and that this would form part of a broader assessment with the patient. However clinician feedback also suggested that to ensure best clinical practice, patients are likely to be assessed for continuation at earlier time points in line with current care (i.e. at one of their bi-annual routine assessments) to ensure the efficacy and safety benefit remain favourable for the patient being reviewed. An earlier review has not been captured in the model which could mean that the presented results provide an overestimate of the true cost-effectiveness of mepolizumab (as patients with a lower level of effectiveness with associated costs will continue on treatment for longer).

Omalizumab
The omalizumab SmPC states that *"At 16 weeks after commencing Xolair therapy patients should be assessed by their physician for treatment effectiveness before further injections are administered. The decision to continue Xolair following the 16-week time point, or on subsequent occasions, should be based on whether a marked improvement in overall asthma control is seen".*[138] This decision is based upon assessment by the treating physicians using the Global Evaluation of Treatment Effectiveness (GETE) 5 point scale (complete control = 5 [excellent] to a worsening of asthma = 1; responders indicated by an 'excellent/good' rating) as well as clinical judgment of the patient, patient notes and diary data (when available), response indicators such as the ACT (≥2 pt improvement) or mini AQLQ (≥0.5 improvement) and supportive response indicators such as lung function, number and severity of exacerbations and unscheduled health care visits[138]. From clinical advisory board feedback, we know that in clinical practice patients initiated on omalizumab are followed up at 16 weeks for assessment of treatment continuation.

Over time the proportion of 'responders' at 16 weeks has increased. In the RCT setting this was reported at 56.5%[58,152] and in an open label setting 70% (see section 5.3 for a summary of omalizumab model inputs describing the percentage responder values explored).[74,152]

5.3 Clinical parameters and variables

Clinical data (exacerbation rates and day-to-day quality of life) were derived from two mepolizumab trials DREAM and MENSA (published and unpublished data) and relevant omalizumab trials (INNOVATE[58] and EXALT[74]). Inputs were extracted from head-to-head trials (add-on mepolizumab versus SoC alone) or estimated by means of a network meta-analysis (mepolizumab versus omalizumab, see section 4.10). Where possible the 75mg IV arm and 100mg SC arms of MENSA were pooled to increase the certainty in the treatment effectiveness, given the doses were deemed bioequivalent (see Section 4.7.3.2). Lastly, asthma-related mortality was extracted from published peer reviewed sources and all-cause mortality was applied from life tables.

Two advisory boards (see Section 2.6 and Appendix 8.1) took place in March and July 2015 with the aim to assess the applicability of the mepolizumab clinical trial data and its relevant to the UK and secondly to test the structure and clinical data and assumptions that underpin the economic model.

5.3.1 Patient characteristics

Table 101 shows the baseline characteristics implemented in the model which were derived from MENSA. At baseline the mean age was 50.1 years and 57.1% of patients were female. For a full description of the baseline characteristics refer to Sections 4.5.2.

Table 101 Patient characteristics at baseline, inputed into model

Characteristics	Value inputed	Source
Age	50.1 years	MENSA
% males/females	42.9% / 57.1%	MENSA

5.3.2 Clinically significant exacerbations

Add-on mepolizumab compared with SoC alone

Head-to-head evidence was used in the comparison of add-on mepolizumab vs. SoC alone. A clinically significant exacerbation is defined in MENSA by a worsening of asthma which requires use of systemic corticosteroids and/or hospitalisation and/or Emergency Department (ED) visits. Use of systemic corticosteroids was defined as intravenous (IV) or oral steroid (e.g. prednisolone) for at least 3 days or a single intramuscular (IM) dose. For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days was required.

The risk of having a clinically significant exacerbation was calculated using the total number of exacerbations divided by the person-years of exposure to obtain a rate per year per comparator. Subsequently, to obtain the exacerbation rate to be inputted into the model, the annual clinically significant exacerbation rates were transformed to 4-weekly (cycle length) rates (Table 102). Up to the 12 months treatment continuation review, people on mepolizumab experience the treatment effect observed for all people randomised to mepolizumab in MENSA (i.e. 0.093 exacerbations per 4 weeks for mepolizumab and 0.204 per 4 weeks for SoC (for the GSK proposed population)).

Table 102: Clinically significant exacerbation rates per comparator, extracted from MENSA (75mg IV+100mg SC arms).

Comparator	Full Trial Population (ITT of MENSA)		GSK proposed population excluding mOCS users with <4 exacerbations		GSK proposed population	
	Annual rate	4-week rate	Annual rate	4-week rate	Annual rate	4-week rate
Add-on Mepolizumab	0.877	0.067	1.213	0.093	1.206	0.093
SoC	1.744	0.134	3.101	0.239	2.650	0.204

After the treatment continuation review, the cohort is separated into patients meeting and not meeting the continuation criteria. This means that patients who experience an increase in annualised exacerbation rate from that observed at baseline are discontinued from mepolizumab. Patients who experience no change in annualised exacerbation rate or who experience an improvement over baseline rates continue on mepolizumab.

Patient level data from MENSA at 32 weeks were analysed to determine those patients meeting the 12 month exacerbation continuation criteria and their corresponding exacerbation rate was applied at 12 months in the model (see Table 103). Patients not meeting the continuation criteria revert back to SoC alone and experience the exacerbation rates of the SoC group from that point forward i.e. 0.204 per 4 weeks (as outlined in Table 102).

Table 103: Clinically significant exacerbation rates for patients on add-on mepolizumab meeting the exacerbation continuation assessment at 12 months, derived from MENSA at 32 weeks (75mg IV + 100mg SC)

Continuation criteria	Full Trial Population (ITT from MENSA)		GSK proposed population excluding mOCS users with <4 exacerbations		GSK proposed population	
	Annual rate	4-week rate	Annual rate	4-week rate	Annual rate	4-week rate
Exacerbation rate applied post-12 months in the model for those patients meting the exacerbation continuation criteria	0.550	0.042	0.723	0.056	0.645	0.050

Table 104 presents the proportion of patients who continue on mepolizumab, upon meeting the exacerbation continuation criteria (i.e. the 'transition probability' from moving to the continuation on biologic therapy state and 1-P, the probability of discontinuing on biologic therapy. For the GSK proposed population 92.3% of patients continued on add-on mepolizumab at 12 months and therefore 7.7% discontinued.

Table 104: Proportion of add-on mepolizumab patients meeting continuation criteria, MENSA

Continuation criteria	Full Trial Population (ITT from MENSA)			GSK proposed population excluding mOCS users with <4 exacerbations			GSK proposed population		
	n	N	%	n	N	%	n	N	%
Proportion of patients meeting the exacerbation continuation criteria at 12	350	385	90.9%	99	102	97.1%	132	143	92.3%

months									

The distribution of type of exacerbations was found to be independent of treatment, and only varies in proportion by sub-population (see Table 105). For the GSK proposed populations the proportion of exacerbations resulting in an ED visit or a hospitalisation exceeded 10% each. Specifically for the GSK proposed population 78.1% of exacerbations required an OCS burst, 10.5% an ED visit and 11.4% a hospitalisation.

Table 105: Distribution by type of exacerbation MENSA (75mg IV and 100mg SC)

Type of exacerbation	Full Trial Population (ITT from MENSA)			GSK proposed population excluding mOCS users with <4 exacerbations			GSK proposed population		
	n	N	%	n	N	%	n	N	%
OCS burst	373	449	83.1%	127	166	76.5%	164	210	78.1%
ED visit	39	449	8.7%	18	166	10.8%	22	210	10.5%
Hospitalisation	37	449	8.2%	21	166	12.7%	24	210	11.4%

Add-on mepolizumab compared with add-on omalizumab (overlap)

A network meta-analysis was conducted to estimate the relative exacerbation rates of add-on mepolizumab compared with add-on omalizumab. Given the limitation of the available evidence for omalizumab, the comparison versus omalizumab was made in the full trial population (see section 4.10). The results showed that mepolizumab was at least as effective as omalizumab for the three end points considered (clinically significant exacerbations, hospitalised exacerbations and change from baseline in predicted FEV_1). It is therefore deemed a reasonable assumption that in the true overlap population add-on mepolizumab would remain at least as effective as add-on omalizumab and therefore the results for the full trial populations are still informative for the Decision Problem. The corresponding rate ratios versus placebo for clinically significant exacerbations were found to be 0.496 for add-on mepolizumab and 0.746 for add on omalizumab (Table 106). The RRs were applied to the baseline exacerbation rate of SoC (Table 102).

Table 106: Relative and absolute exacerbation rates resulting from the network meta-analysis (clinically significant exacerbations as defined in the network meta-analysis)

Comparator	RR vs. Placebo	Upper 95% Cr In	Lower 95% Cr In	Annual rate	4-week rate
Add-on Mepolizumab	0.496	0.407	0.603	NA	0.101
Add-on omalizumab	0.746	0.630	0.883	NA	0.152

Omalizumab also has stopping criteria based on an assessment at 16 weeks (section 5.2.4). As the treatment continuation reviews are defined differently for mepolizumab and omalizumab, exacerbation rates of those who continue or discontinue treatment could not be indirectly compared. For omalizumab, these values were taken from the literature (reviewing those studies extracted from the systematic literature review, see section 4.1). Consistent with the omalizumab NICE MTA (TA 278), Global Evaluation of Treatment Effectiveness (GETE) was identified in 4 RCTs (INNOVATE [28 weeks][58], EXHALT [32 weeks][74] and supportive trials SOLAR [28 weeks][85] and Bardelas 2012 [26 weeks][63]).

For the base case INNOVATE[58] was considered to be most relevant source from which to determine the rate of exacerbations post continuation assessment for people treated with omalizumab because it is the only double-blind RCT in which the GETE has been used to assess response to treatment and where a responder analysis is available (reported in the NICE Assessment Group's publication, Norman 2013[152] and not the primary publication for INNOVATE, Humbert 2005[58]). A summary of the post-continuation omalizumab data implemented in the model is provided in Table 107.

Table 107: Exacerbation rate post-continuation assessment and proportion of 'responders' for omalizumab

INNOVATE*				
	Ln (RR) vs. Plc	**RR vs. Plc**	**Annual rate**	**4-week rate**
Add-on omalizumab: meeting continuation criteria	-0.986	0.373	NA	0.076
	n	**N**	**p (%)**	
Proportion meeting continuation criteria	118	209	56.5%	
EXALT*				
	Ln (RR) vs. Plc	**RR vs. Plc**	**Annual rate**	**4-week rate**
Add-on omalizumab: All patients	-0.562	0.570	NA	0.116
Add-on omalizumab: meeting continuation criteria	-0.892	0.410	NA	0.083
	n	**N**	**p (%)**	
Proportion meeting continuation criteria	190	271	70.1%	

* The results of the post-hoc analysis were not presented in the original trial publications and taken and implemented from the HTA independent assessment.[152]

Treatment efficacy by response status was also available from EXALT[74]; however, the open-label design of EXALT makes the trial more susceptible to a number of potential biases. A scenario analysis was conducted to explore the sensitivity of the cost-effectiveness results to different efficacy estimates by using the treatment effect observed in EXALT. Model inputs are shown in Table 107 and a summary of INNOVATE and EXALT trials is provided in appendix 8.11.

5.3.3 Discontinuations beyond 12 months

We assume that patients continue on mepolizumab for 10 years which is consistent with the approach taken in the recent NICE MTA of omalizumab[170] and supported by clinician feedback. From discussion with clinicians at advisory boards, in practice, patients on mepolizumab will continue to be followed up at routine out-patient appointments over time to ensure that the benefit and safety profile is still favourable for the patient. Besides any formal continuation criteria, there may also be additional reasons why a patient discontinues treatment with a biologic such as personal preference, or difficulty attending administrations etc.

In recognition of this likely natural attrition rate over time (i.e. not all patient continuations beyond 12 months will continue on mepolizumab for the full 10 years) we have modelled a 10% attrition rate year on year post-12 months. In the mepolizumab clinical trial programme, attrition ranged from 5-16%: in DREAM, a 52

week study, 16% discontinued (96/616), in MENSA, a 32-week study, 6% of patients withdrew from the study (37/576), in SIRIUS, a 24 week study 5% of patients (7/135) and in the one year OLE study, COSMOS, 10% of patients withdrew from treatment with mepolizumab (66/651). Reasons cited included lack of efficacy (exacerbation), protocol deviation (e.g. pregnancy) and lost to follow-up. Discontinuation rates in clinical practice may be higher than that modelled and seen in the clinical trials in which people are encouraged / more personally motivated to remain on treatment (especially where there are limited treatment options outside of the trial).

The proportion of patients who discontinue from add-on omalizumab ranges from approximately 8.5%[171] to 34%[103]. We have assumed the same rate of discontinuation (10% year-on-year) for patients on omalizumab as those on mepolizumab.

5.3.4 Compliance and adherence to treatment

For both add-on mepolizumab and add-on omalizumab treatment compliance and adherence is assumed to be 100% for those patients who continue on biologic therapy since treatment occurs at regular intervals in a clinical setting. This is consistent with the assumption made in the omalizumab NICE MTA TA278[152]. People deemed at high risk of severe asthma attacks should be monitored more closely as part of their personal asthma action plans.[49] We do recognise that in practice not everyone is likely to be compliant.

5.3.5 Persistence of treatment effect

For those patients who continue on mepolizumab for the duration of 10 years, it is assumed that they continue to experience the same reduction in exacerbations to that observed post the continuation assessment. In the one year OLE study, COSMOS, the reduction in exacerbations continued. The annualised rate of exacerbations in 651 patients was 0.93 (95% 0.83, 1.04). Specifically for those patients previously on Soc alone/placebo the rate was 0.99 (95% CI 0.83, 1.18), and for those previously on mepolizumab 0.90 (95% 0.78, 1.04). It is anticipated that those patients that do not exhibit continued efficacy relative to the safety profile of mepolizumab would be discontinued from therapy at one of the routine follow-up outpatient attendances. This is assumed to be captured in the economic evaluation through the year on year natural attrition rate applied post 12 months, up to 10 years on treatment.

For patients on omalizumab the same approach is taken. PERSIST[103], a prospective, open-label, observational, multicenter study in patients with severe persistent allergic asthma treated with omalizumab (52 weeks) reported that 82.4% of the ITT population (n=153) were considered responders at 16 weeks, whereas 72.3% of the ITT population (n=130) were considered responders at 52 weeks. Again, it was considered that in clinical practice, a decline in efficacy would trigger a decision to terminate treatment.

Once a patient discontinues mepolizumab, be that at 12 months or as part of the year on year natural attrition rate, no persistence of treatment effect is assumed. In a follow-up analysis to a 50-week study[52] (N=61) where people with severe refractory eosinophilic asthma and a history of recurrent severe exacerbations

subjects received infusions of either mepolizumab, (n=29), or placebo (n=32) at monthly intervals for 1 year, patients were followed up for a further 12 months with assessments every three months.[172] The aim was to examine the change in clinical markers of asthma control following cessation of mepolizumab therapy. Cessation of mepolizumab was associated with a rise in the blood eosinophil count beginning soon after stopping therapy and continuing to baseline over 6 months. The frequency of severe exacerbations increased and 12 months after stopping mepolizumab, exacerbation frequency was not significantly different between subjects previously on mepolizumab and SoC arms.[172]

5.3.6 Mortality

Asthma-related mortality

Limited evidence on mortality in severe refractory eosinophilic asthma patients is captured by the mepolizumab clinical trial programme, nonetheless asthma fatalities are still known to occur (refer to Section 3.5). In previous economic evaluations of omalizumab, asthma-related mortality was identified as one of the key drivers of the cost-effectiveness vs. SoC alone.[152,159] In the economic model, asthma related-mortality is captured by a probability of dying related to experiencing an exacerbation. The source of mortality data is taken from Watson 2007[167] and the NRAD report.[49]

A systematic literature review of asthma-related mortality was conducted to identify UK studies reporting mortality rates as a result of severe asthma, or risk factors for asthma-related death. The systematic review search strategy, inclusion and exclusion criteria and identified studies is provided in Appendix 8.12. In total 47 studies were selected for data extraction, however since this was a global systematic review, only 9 studies were UK based and deemed relevant to this appraisal. On further inspection, of these nine studies only 2 were deemed informative, Watson 2007[167] and Roberts 2013.[173] Details of all 9 studies are provided in Appendix 8.12 including the reason for inclusion or exclusion in this evaluation. For full details refer to the systematic review of economic evidence provided in the reference pack.[164]

i) Basecase mortality assumption: Watson et al., 2007[167] + NRAD[49]

The basecase analysis uses data from Watson 2007 and the NRAD report. The study by Watson et al. was the only study to report mortality risk for acute severe asthma patients hospitalised for asthma. Data was analysed from the CHKS database, specifically admissions with ICD10 codes J45 (asthma, plus sub-codes J45.0, J45.1, J45.8 and J45.9) and J46 (acute severe asthma). Mortality during the admission spell (the period from a live admission to either discharge or death) was then recorded by admission code and stratified by age band (<12, 12–16, 17–44 and ≥45 years) and gender. One of the key limitations with this study is that in the absence of a death certificate the death could not be attributed to asthma with any certainty. However it was deemed reasonable by Watson et al to assume that asthma was at least a contributory factor in the majority of deaths due to death occurring in the same admission spell, which lasted only a few days in the majority of patients. Time between admission and death was 4 days in acute severe asthma patients. Additionally no secondary morbidity codes were reported for the patient in over 80% of cases.

The mortality risk reported by Watson et al. is a conditional probability; it represents the probability of death given a hospitalisation for asthma (see Table 108). In order to obtain the asthma-related mortality risk for the economic analysis, the mortality risk following hospitalisation is multiplied by the risk of a clinically significant exacerbation requiring a hospitalisation. Therefore, the age dependent risks are only applied following an exacerbation requiring hospitalisation.

Table 108: Probability of mortality following an exacerbation requiring hospitalisation, taken from Watson et al., 2007[167]

Age group	N death in those patients with acute severe asthma (J46)	N hospitalised in those patients with acute severe asthma (J46)	p (%) applied to the rate of exacerbations requiring a hospitalisation
<12	8	8,222	0.10%
12-16	5	1,568	0.32%
17-44	36	9,407	0.38%
≥45	177	7,143	2.48%

Applying only an asthma related mortality risk to those experiencing an exacerbation requiring a hospitalisation was deemed a conservative approach as it is known that patients die of asthma exacerbations outside of the hospital setting. The NRAD[49] report (identified through hand searching) is the first UK wide investigation into asthma deaths and the largest worldwide study of this kind to date. The aim was to understand circumstances surrounding asthma deaths and to identify avoidable factors and make recommendations for change and improvement in asthma care. The study was undertaken over a three year period (2011-2014). Extensive information about each death was sought from multiple sources including primary, secondary and tertiary care, as well as ambulance, paramedic and out of hours care providers. Death by location showed that 41% died at home, 23% on the way to hospital and 30% in hospital. Forty-five per cent (87/195) died from asthma without any medical assistance during the final episode; for 65 of these cases, there was no record of them seeking medical assistance, and for 22 cases (11%), there was a record of the patient trying to get help but dying before medical treatment could be provided.

Of 155 patients for whom severity could be estimated, 61/155 (39%) appeared to have severe asthma. Fourteen (9%) were being treated for mild asthma and 76 (49%) for moderate asthma. The report suggested that many patients who were treated as having mild or moderate asthma had poorly controlled undertreated asthma, rather than truly mild or moderate disease.

NRAD is considered a valuable source of proxy mortality data for non-hospitalised mortality. It allows an estimation of probability of death for non-hospitalised exacerbation by combining location of death information with probabilities for death for hospitalised exacerbation (Watson 2007). The probability of death following an OCS or ED exacerbation is calculated as follows (as an example):

Hospitalised exacerbation as a proportion of total exacerbation * probability of death following a hospitalised exacerbation / proportion of death which occurs in hospital) * (proportion of death which occur in the community / OCS exacerbations as a proportion of total exacerbations) = probability of death following an OCS exacerbation

(0.082 * 0.0248 / 0.303) * (0.467 / 0.831) = 0.0039

Therefore whilst mortality associated with hospitalised exacerbations is derived from Watson 2007, the estimated mortality for non-hospitalised exacerbations which is estimated from NRAD takes into account the proportion of hospitalised exacerbations.

We do recognise that there are limitations in using NRAD as a source of non-hospitalised mortality. NRAD data is not in an exclusively severe asthma patient population. Speculatively, there may be a greater proportion of death in the hospital in a more severe cohort as those patients may be more familiar with the signs of symptomatic worsening, whereas a milder patient may not recognise the severity of their exacerbation and thus be more likely to die at home before receiving professional intervention. Secondly, assumptions have been made about the location of deaths and their relevance to the modelled exacerbation sub-types. Hospitalised death is reported but we make the assumption that pre-hospital arrest (i.e. dying on the way to hospital; ambulance) deaths are equivalent to emergency room and that the remainder of death that occur in the community are equivalent to the OCS burst exacerbation sub-type. However, it was felt that even with these assumptions it was more clinically plausible and more reflective of the real-world reality that there would be a probability of death associated with non-hospitalised exacerbations and therefore have made an attempt to account for this utilising insights from NRAD. Table 109 shows the inputted asthma related mortality values.

Table 109 NRAD as a proxy for mortality related to exacerbations requiring an OCS burst or ED visit

NRAD report		Application in the model	
Location of death (taken from Table 4.4.1, NRAD)	**N(%)**	**Proxy for type of exacerbation**	**Probability of death**
Home	80(41)	Exacerbation: OCS burst	<12 y = 0.0001
Nursing/residential home	5(3)		12-16 y = 0.0005
Holiday	4(2)		17-44 y = 0.0006
Other	2(1)		≥45 y = 0.0038
Hospital, pre-hospital arrest	45(23)	Exacerbation: ED visit	<12 y = 0.0007
			12-16 y = 0.0023
			17-44 y = 0.0028
			≥45 y = 0.0179
Hospital, arrest in hospital	59(30)	Exacerbation: hospitalised	Watson 2007 applied, see above assumptions

ii) Mortality scenario analysis: Watson only
Asthma related death from Watson 2007 is applied only to those patients experiencing an exacerbation requiring a hospitalisation, i.e. exclusion of proxies for non-hospitalised exacerbations. This uses values described in Table 108.

iii) Mortality scenario analysis: NICE omalizumab MTA (TA278) – approximated approach; Watson 2007 + De Vries 2011 + 15%

Note that in the systematic review undertaken, De Vries et al (2010)[168] was not included since the study reports the risk of asthma death from medication use (LABA, SABA, ICS) and not asthma mortality in general. De Vries was the source of the mortality assumptions applied in the NICE MTA of omalizumab (TA 278, Assessment Group's model). De Vries et al used the primary care GPRD database (from January 1993) to describe the patterns of risks of death and asthma outcomes with exposure to different asthma medications in general practice and then to compare the patterns of risks of death and asthma outcomes between LABA, inhaled short-acting b2- agonists (SABA) and ICS. Unlike Watson et al., De Vries evaluated the cause of death from free text entries at the date of death, as well as a review of the clinical records for appropriate medical codes ≤21 days (before and after) of the date of death. However the study was conducted by treatment step and therefore included both controlled and uncontrolled patients.

Comparing the two sources the Assessment Group identified that the risk of mortality was similar for patients aged 12-44 years but for patients ≥45 years the risk of asthma related death reported in De Vries was about one fifth of the risk reported by Watson. However this was considered consistent with Watson since approximately 20% of the clinical significant severe exacerbations in INNOVATE involved hospitalisation.[152] De Vries (2010) was chosen by the Assessment Group since the GPRD study reported data stratified by severity and included deaths in the community.[170] The probability of asthma related mortality over a 3 month cycle (using date from De Vries) was 0.001 which was applied to the whole cohort (0.4 deaths per 100 person-years).[170] In the final assumptions a mortality risk which represented the mid-point of Watson and De Vries plus 15 % was implemented.[137]

We have attempted to replicate this approach as a scenario analysis however there are differences between the mepolizumab and omalizumab models, namely that in the omalizumab model exacerbations were deemed separate health states and not transient events as in the mepolizumab model, and differences in the rate of exacerbation types and definitions of these exacerbations.

Our approximation of this approach is as follows. Asthma related mortality was calculated by age band from both Watson 2007 and De Vries 2011. Then, 15% was added and the average was taken across the two studies and the resultant probabilities were reverted back by age weighting. This is provided in Table 110.

Table 110 Estimated probability of asthma related death derived from Watson 2007, De Vries 2011 with and without + 15% (approximated NICE approach)

Age of patient	Probability of death (applied to all patients experiencing an exacerbation) + 15%	Probability of death (applied to all patients experiencing an exacerbation) not incl. + 15%
<12 y	0.0007	0.0006
12-16 y	0.0022	0.0019
17-44 y	0.0027	0.0023
≥45 y	0.0174	0.0151

iv) *Mortality scenario analysis: NICE omalizumab MTA (TA278) – approximated approach; Watson 2007 + De Vries 2011 not including 15%*
For completeness we also apply the NICE approximated approach as described above without the additional 15% risk.

v) *Mortality scenario analysis: Roberts 2013*[173]
Alternatively, in another scenario analysis data from Roberts 2013 (identified from the systematic review) is applied. The study investigated the risk of 30 day case-fatality following hospitalisation for asthma in adults in Scotland from 1981 to 2009. The Scottish Morbidity Record Scheme with all asthma hospitalisations for adults (>18 years) with ICD9 493 and ICD10 J45-J46 in the principal diagnostic position at discharge was used. These data were linked to mortality data from the General Register Office for Scotland, with asthma case-fatality defined as death within 30 days of asthma admission (in or out of hospital). The limitations for applicability of the data in the economic model are that case fatality by patients with severe asthma is not specifically defined neither is the time over which the analysis completed; care and consequently outcomes are likely to have changed over the 28 year study period. Further, the absolute risks were not reported and therefore the absolute deaths per age group were estimated based on the total numbers of deaths (n=1000) and the unadjusted odds ratios reported in order to calculate risk ratios. The estimated numbers deviate slightly from the real observed data due to the fact the rounded (1 decimal) odds ratios were reported. The application of the calculated probabilities derived from Roberts 2013 is explored in a scenario analysis and inputs are shown in Table 111.

Table 111: Probability of mortality following an exacerbation requiring hospitalisation, from Roberts 2013[173]

Age group	N death	N hospitalised	p (%) applied to the rate of exacerbations requiring a hospitalisation
18-24	25*	17,173	0.15%
25-34	30*	20,785	0.14%
35-44	41*	20,390	0.20%
45-54	89*	19,856	0.45%
55-64	210*	16,474	1.27%
≥65	605*	21,779	2.78%

*Estimated numbers based on total number of deaths and the unadjusted odds ratios

All-cause mortality
The risk of other cause mortality was estimated using UK age- and sex-specific mortality risks based on national life-tables for the UK for the years 2011-13.[174] The data were applied to all health states in the model. Asthma related deaths were not removed from all-cause mortality since the small number of asthma deaths in the general population, was deemed unlikely to impact the results.

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

The EQ-5D was not collected in the phase III trials for mepolizumab. HRQL was measured in Phase IIb DREAM (AQLQ and EQ-5D), Phase III MENSA (SGRQ) and Phase III SIRIUS (SGRQ). The assessment schedule is described in section 4.3 and the results are described in section 4.7.

Selection of SGRQ derived utilities over EQ-5D
The generic choice based EQ-5D represents the NICE reference case however the EQ-5D values are not implemented in the base case of the economic evaluation. EQ-5D was captured at 4-weekly intervals in the 52 week dose ranging Phase IIb DREAM. Our rationale for this is as follows:

At baseline approximately a third of patients in DREAM reported an EQ-5D utility score of 1.0, although they met the clinical trial inclusion criteria. This is unusual for a severe patient cohort and meant that for this group of patients no improvement in health status was possible as a result of mepolizumab therapy. This does not reflect the impact of severe asthma on the quality of life of this patient population as described by respiratory clinicians. Furthermore for those patients experiencing ≥ 4 exacerbations in the previous 12 months the EQ-5D differential between mepolizumab and SoC was worse than in the ITT population suggestive of poor sensitivity in severe asthma (there were no instances of this in SGRQ derived values). These observations also question the construct validity in this setting. Indeed, the EQ-5D suffers from known ceiling effects across a number of disease populations including in asthma cohorts.[175-177] The EQ-5D (3L version) has been demonstrated to be less responsive than disease specific measures in asthma populations.[121] Because in earlier trials EQ-5D did not capture the granularity in HRQL of people with severe asthma, it was therefore not incorporated into the later Phase III programme (MENSA and SIRIUS).

The basecase therefore includes SGRQ derived utility values which are an appropriate source to reflect the background health status. The SGRQ is a disease specific questionnaire that assesses health in chronic airflow limitation and is designed to measure health impairment in patients with asthma and COPD.[124] While it has been used more frequently in COPD, SGRQ is validated for use in asthma and has been used in severe asthma.[131,132,158,178] SGRQ has recently been shown by independent investigators to be effective in measuring health status of patients with severe asthma. In a cohort of severe asthma patients, the SGRQ discriminated between patients with frequent exacerbations (≥2) compared to those with few (<2) exacerbations.[131] In addition, in a study of patients with severe, uncontrolled asthma in Brazil,[132] the SGRQ total and domain scores were strongly correlated with both the ACQ and Asthma Control Test (ACT).

Compared to the five items of EQ-5D, SQRQ includes 50 items with 72 weighted responses[179] covering frequency of respiratory symptoms (part 1) and a patient's current state (part 2). Part 2 provides an activity score (disturbances in daily physical activity) and an impact score relating to psycho-social functioning disturbances. SGRQ includes a number of dimensions considered likely to be important to people with severe asthma which are not captured in EQ-5D such as how taking medication makes the patient feel, what activities are impacted by breathlessness and how activities may be affected by a patient's breathing.

The SGRQ demonstrated significant treatment differences in both MENSA and SIRIUS, where the mean difference versus SoC alone exceeded the MCID (≥4 point reduction) (see section 4.7). The longer recall period of the SGRQ (up to a year in part 1 and 'these days' in part 2) versus the EQ-5D (in the moment) may have allowed for a greater impact and change to be captured. In the base case of the

economic evaluation, utility derived from SGRQ values collected in the phase III trial MENSA (mapped to EQ-5D) are implemented. A scenario analysis utilising directly elicited EQ-5D values from the Phase IIb study DREAM is presented for completeness.

One element of HRQL not captured, common across all HRQL instruments is the decrement of HRQL experienced during an exacerbation. This is addressed in section 5.4.3. There are also other elements of HRQL unlikely to be captured by such instruments including fear of an exacerbation and the impact of an exacerbation not only for the patient but also the carer.

5.4.2 Mapping

SGRQ data was measured at baseline and at the end of the MENSA trial, and utility values were calculated by mapping of the SGRQ to EQ-5D, using an algorithm estimated in a COPD population:[180]

- Data from MENSA are mapped from SGRQ total score using EQ-5D = 0.9617 - 0.0013 × SGRQ total - 0.0001 × SGRQ total^2 + 0.0231 × male [OLS model]

Starkie et al. used EQ-5D and SGRQ data collected between weeks 24 and 3 years from a large COPD study (TORCH; Towards a Revolution in COPD Health). A number of models were evaluated (OLS, GLMs, two-part models) and the OLS model was deemed the best fit (RMSE = 0.1723). Starkie et al showed that QALYs estimated using the mapping algorithm were marginally higher than the QALYs using the EQ-5D data directly; however the results were broadly comparable. It should be noted that there is precedent for this COPD mapping algorithm being implemented in a non-COPD patient population as in the recent NICE TA (TA282) for idiopathic pulmonary fibrosis.[181] The inputted SGRQ utility values are summarised in Table 113.

5.4.3 Health-related quality-of-life studies

An independent systematic literature review was conducted to identify relevant HRQL data. The databases were searched for HRQL and utility studies. Details of the search strategies are provided in Appendix 8.13, and the full systematic review report is provided in the reference pack[182]. The search was conducted on 18th May 2015 (an update to original searches conducted on 16-17th June 2014) and yielded 2,738 unique publications. Of these, 335 articles were deemed relevant for full text review. In total 87 publications (of which 14 articles were identified from either the grey literature [6] or through a review of HTA sites [8]) were included after full text assessment. Of note, the severity of asthma in the evaluated populations was based on a wide range of international asthma guidelines and study specific criteria (please refer to systematic review report).

The range of tools used to assess HRQL across the studies generally included more than one PRO instrument. Among studies evaluating patients with asthma-specific PRO instruments, the most frequently reported instrument was the Asthma Control Questionnaire (ACQ) reported in 45 studies and the Asthma Quality of Life Questionnaire (AQLQ), found in 42 studies. SGRQ was utilised in 7 studies.[55,56,136,183-187] Not surprisingly, HRQL in patients with severe and/or

eosinophilic asthma compared with those who had less severe disease was poorer as evaluated by the SGRQ.[183] In one study, people with severe asthma experiencing exacerbations reported poorer HRQL using the SGRQ.[184]

For studies that analysed HRQL using generic instruments, the most frequently utilised PROs were EQ-5D (15 studies) and the Medical Outcomes Survey Short Form (SF-36) (5 studies). The Asthma Control Questionnaire (ACQ) (24 studies) and Asthma Control Test (ACT) (8 studies) were the most frequently used instruments to assess asthma control in patients.

Published utility data are summarised in Appendix 8.13. Only two publications (one of which was a HTA assessment) were identified that included direct preference elicitation methods.[183,188] Results from indirect preference elicitation methods which yielded 10 studies,[137,183,188-195] suggested that patients with a poorer health status had lower utility values compared with those of a better health status. This appeared to be true regardless of how health status was evaluated (presence of symptoms, control of symptoms, and experience of exacerbations, or lung function). Overall, utility values for patients reporting symptoms was lower regardless of treatment and varied from 0.669–0.85 compared with 0.91–0.97 in patients reporting no symptoms.[188] A similar trend was observed for patients who had poorer control (range: 0.48–0.63) compared with those with better control (range: 0.78–0.92), and those with reduced %FEV_1 compared with those with close to normal lung function.[188] Furthermore, patients who had an exacerbation typically had lower utility (0.57), particularly those who experienced severe exacerbations (0.33).[188-191]

In the omalizumab NICE MTA, two sources of utility are referred to.[152] The manufacturer mapped AQLQ (captured in INNOVATE) and mapped to EQ-5D which for the ITT produced a utility difference of 0.11 (0.669 for patients on SoC and 0.779 for responder patients on add-on omalizumab). The assessment group preferred to use directly elicited EQ-5D values from EXALT despite the observational nature of this trial which likely introduced bias. For the ITT this resulted in a difference of 0.048 between arms (0.719 for those of SoC compared with 0.767 for those responding on add-on omalizumab).

SGRQ derived utilities, taken from MENSA and mapped to EQ-5D, for the GSK proposed population showed a difference of 0.069 (0.708 for patients on SoC and 0.777 for patients on add-on mepolizumab). For patients who continue on mepolizumab (post the continuation criteria) the difference increases to 0.087 (0.708 for patients on SoC and 0.795 for patients who continue on add-on mepolizumab). Inputted values used in the model are provided in Table 113.

The other key purpose of this review was to identify relevant utility values to represent the decrement in quality of life associated with an exacerbation event. The review identified one study of interest Lloyd et al., 2007.[165] Lloyd et al conducted a prospective observational study to capture the HRQL burden associated with an exacerbation event in moderate to severe asthma patients in the UK (Step 4 and Step 5 of the BTS/SIGN guidelines)[22]. The HRQL life data was collected over four weeks to accurately capture the burden of an exacerbation. Patients completed three instruments at baseline and at the end of four weeks: mAQLQ, EQ-5D and the ASUI. In total 112 patients were recruited across 4 UK centres and categorised into

three groups: No exacerbations (N=85), Exacerbation, no hospitalisation (N=22), Exacerbation with hospitalisation (N=5). Across the three groups the mean age of patients ranged from 40.5 years to 48.4 years with between 60%-72.7% female. All instruments demonstrated a worsening in HRQL for patients experiencing an exacerbation (p<0.001) compared to those experiencing no exacerbation. The results captured on EQ-5D utility are summarised in Table 112. The same approach was taken in the omalizumab NICE MTA[152]; the reported decrement in utility was applied to the day-to-day utility score for a duration of 28 days (see Table 114) which reflects the time over which EQ-5D was captured in Lloyd.

Table 112 EQ-5D data captured (Lloyd et al., 2007) at final study visit

Type of exacerbation	Mean (SD)	Mean change from baseline
No exacerbation	0.89 (0.15)	0.02
Exacerbation requiring OCS	0.57 (0.36)	-0.10
Exacerbation requiring hospitalisation	0.33 (0.39)	-0.20

5.4.4 Adverse reactions

Across DREAM, MENSA and SIRIUS a total of 915 patients received at least one dose of mepolizumab. Section 4.12 showed the proportion of subjects experiencing most common on treatment AEs and corresponding event events across the placebo controlled severe asthma studies (PCSAs). The integrated safety summary showed that the incidence of AEs was similar for the placebo group (82%) compared with the mepolizumab 100mg SC (79%) and 75mg IV (83%). Headache (18% in the placebo group, 20% in the mepolizumab 100mg SC group and 23% in the 75mg IV group) and nasopharyngitis (19% in the placebo group, 16% in the mepolizumab 100mg SC group and 23% in the 75mg IV group) were the most frequently reported AEs. The incidence of injection site reactions with mepolizumab 100mg SC and placebo was 8% and 3% respectively; all non-serious and the majority resolved in a few days. A total of 35 patients reported AEs leading to withdrawal (3% in the placebo group, 1% in the mepolizumab 100mg SC group and 1% in the 75mg IV group).

For omalizumab (INNOVATE)[58] the overall incidence of AEs was similar for omalizumab (72.2%) and placebo arms (75.5%). The most common AEs were lower respiratory tract infections (omalizumab 27 [11%] compared with placebo 24 [10.1%]), nasopharyngitis (24 [9.8%] compared with 22 [9.3%]) and headaches (17 [6.9%] compared with 22 [9.3%]) respectively. The total incidence of injection site reactions was higher in the omalizumab group (5.3%) than the placebo group (1.3%). Because of these small proportions and minor differences between treatment groups, no adverse events were included in the model and this is consistent with previous economic analyses.[152,159]

5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

In the base case analysis, for day-to-day symptoms (which includes any occurrences of symptom-free periods as well as non-clinically significant exacerbations (morning, night time and day time symptoms)), utility is derived from SGRQ mapped to EQ-5D

(see section 5.4.2). In a scenario analysis the impact of using EQ-5D values captured in DREAM is also explored. A summary of the utility values implemented in the model is shown in Table 113. It is assumed that HRQL remains stable other than on two occasions. Firstly for patients meeting the mepolizumab continuation assessment, their utility improves after 12 months. Secondly the short term (28 days) reduction in HRQL following an exacerbation event. For comparison with omalizumab, omalizumab is assigned the same utility as that for mepolizumab (since an NMA could not be completed on the HRQL end points).

Table 113 Health state utility values implemented in the economic analysis

	Full ITT (MENSA)	GSK proposed population excluding mOCS users with <4 exacerbations	GSK proposed population
State	**Mean (SE)**	**Mean (SE)**	**Mean (SE)**
SGRQ derived utility (Base case), MENSA (IV and SC)			
Add-on mepolizumab: all patients	0.796 (0.010)	0.793 (0.021)	0.777 (0.017)
SoC: all patients	0.738 (0.015)	0.682 (0.038)	0.708 (0.029)
Add-on mepolizumab: Patients continue after assessment of exacerbations from baseline	0.806 (0.009)	0.805 (0.018)	0.795 (0.016)
EQ-5D utility (aggregate)(Scenario analysis), DREAM Phase IIb (IV only)			
Add-on mepolizumab: all patients	0.802 (0.005)	0.829 (0.009)	0.827 (0.007)
SoC: all patients	0.794 (0.005)	0.797 (0.011)	0.785 (0.009)
Add-on mepolizumab: Patients continue after assessment of exacerbations from baseline	0.824 (0.006)	0.834 (0.012)	0.837 (0.009)

*EQ-5D values were aggregated for all timepoints

The decrement in utility associated with an exacerbation event is sourced from Lloyd et al., 2007[165] and summarised in Table 114. Lloyd et al. did not report the utility associated with an exacerbation requiring an ED visit, therefore the EQ-5D value for an exacerbation requiring a burst of OCS use was conservatively used as a proxy for an exacerbation requiring an ED visit in the absence of other relevant data.

Table 114: Utility decrement for exacerbations applied over 28 days (base case).

Exacerbation type	Utility decrement	Source
Exacerbation: OCS burst	-0.10	Lloyd 2007
Exacerbation: ED visit	-0.10	Assumption
Exacerbation: Hospitalisation	-0.20	Lloyd 2007

The duration over which the decrement in utility is applied following an exacerbation is four weeks (28 days) in the base case. This assumption is consistent with the source of the utility decrement (Lloyd 2007) and omalizumab NICE MTA.[152] However, it was noted that the impact of an exacerbation on the HRQL score may not be fully captured if the exacerbation occurred several days or weeks before the data collection time point at week 4. The 28 day duration was tested at two advisory boards and the clinical feedback was that this may over estimate the duration of an

OCS burst exacerbation but likewise may underestimate the duration of an exacerbation requiring a hospitalisation. Applying the decrement for an OCS burst exacerbation to an ED visit was accepted but in most cases was considered a conservative proxy in the absence of further evidence. In a scenario analysis the length of the duration of an exacerbation as captured in MENSA is explored. These alternative assumptions are shown in Table 115.

Table 115: Alternative duration for the utility decrement for exacerbations (scenario analysis)

Exacerbation type	Duration (days)	Source
Exacerbation: OCS burst	12.68	MENSA
Exacerbation: ED visit	10.41	MENSA
Exacerbation: Hospitalisation	20.70	MENSA

It should also be noted that there is an element of double counting which cannot be accounted for. The day-to-day utility as derived from SGRQ theoretically captures disutility associated with an exacerbation, since instrument items ask patients to retrospectively capture their HRQL (i.e. beyond the moment when the instrument is administered). However it does not explicitly capture the HRQL impact of an exacerbation event. Again, this approach is no different than that utilised in the omalizumab NICE MTA.[152] It should also be noted that the decrement in utility for a carer of a patient with severe asthma is also not captured in this evaluation.

5.5 Cost and healthcare resource use identification, measurement and valuation

The principles of costing in the economic evaluation were based on approaches taken in the recent NICE MTA of omalizumab.[152] Specifically the model includes drug acquisition costs, administration costs, monitoring costs and costs associated with exacerbation resolution. Note that mepolizumab is expected to be excluded from the PbR tariff and funded via specialist commissioning. Costs have been identified from NHS reference costs (2013-2014)[196] and PSSRU (2014).[197]

5.5.1 Resource identification, measurement and valuation studies

An independent systematic literature review was conducted to identify relevant health costs and resource utilisation costs associated with severe asthma. This formed part of the same review set out to identify economic evidence (Section 5.1). Please refer to appendix 8.9 for details of the search strategy and the full systematic review of the economic evidence provided in the reference pack.[164] Of the 263 full text articles reviewed, 43 cost and health utilisation studies were identified. For the purpose of this appraisal, only those studies conducted in the UK were deemed relevant for review (six in total). A summary of the 43 studies and details of the 6 UK studies[21,100,198-201] is provided in Appendix 8.14.

Two of the six UK studies were retrospective database studies,[199,200] one study utilised the BTS difficult asthma registry,[21] one used hospital and GP records[100] and two reported on observational studies.[198,201] The mean number of ED visits per year was reported in one study for a population of severe allergic asthmatics (12-84 years) at 1.52 (SD 2.194).[100] The same study reported a mean number of hospitalisations per year of 1.3 (SD 1.731). Two studies reported the mean number

of GP visits per year for people with severe asthma ranging from 2 to 8 visits per year dependent on reported patient compliance.[21,199] The mean daily dose of OCS (on OCS treated days) was reported in one study at 21.4mg.[100]

5.5.2 Intervention and comparators' costs and resource use

Intervention and active comparator drug costs are shown in Table 116. The primary comparator in this appraisal is SoC which is associated with no additional drug costs. Drug cost for omalizumab were based on the list price reported in the British National Formulary.[202]

Table 116: Drug acquisition costs (biologics)

Drug	Strength	Cost/Unit (excluding VAT)	Source
Add-on mepolizumab	100mg	List: £840 PAS price: [redacted]	GSK
		28 day cost implemented in the economic model: List: £840 PAS price: [redacted]	GSK
Add-on omalizumab	75 mg	£128.07	BNF[202]
	150 mg	£256.15	BNF[202]
		28 day cost implemented in the economic model: 1. Base case: £872.22 2. Scenario analysis 1: £617.99 Note: There is a confidential PAS in place for omalizumab – please refer to the confidential addendum to this submission document.	1. IMS Health 2. NICE 2013[152,170]

The unit cost of mepolizumab already reflects the cost per 4-week cycle length, as it is administered once every four weeks for all patients. Omalizumab is administered as a subcutaneous injection every 2 or 4 weeks and the exact dosing depends on a patient's serum IgE and weight. It is available as a 75- or 150-mg pre-filled syringe. The per patient cost of omalizumab can therefore range from approximately £1,665 per patient per year (excluding VAT) for a 75-mg dose administered every 4 weeks to approximately £26,640 per patient per year (excluding VAT) for a 600 mg dose (the maximum recommended dose in the SmPC) administered every 2 weeks.[138]

Estimated average annual cost per adult patient on add-on omalizumab
In the recent NICE MTA for omalizumab, the average per patient cost for adults and adolescents was stated as £8,056/year.[152,170] Communication from local payers suggested that the average annual cost had increased. We therefore undertook a separate study with IMS Health to ascertain the dosing distribution of omalizumab in patients over 18 years old in the secondary care setting in England and thus calculated the average annual per patient cost.

Hospital Treatment Insights (HTI), a retrospective database of 42 hospital trusts in England (N=3.8 M) was used, during the study period from January 2010 to June 2014. The HTI database links and combines Hospital Episode Statistics containing patient diagnoses and episodes of care in hospital with IMS Hospital Pharmacy Audit (HPA) data at the patient level (anonymised; patient counts of <6 are not reported). This linkage is achieved through a UK government service provider (Health and

Social Care Information Centre). Approval of the study protocol was agreed through the HTI governance committee (Independent Scientific and Ethical Advisory Committee).

For inclusion, patients were ≥18 years with a clinical diagnosis of asthma (ICD-10 codes: J45, J46 and J82) and had to have had ≥1 prescription of omalizumab over the study period (ATC code R03X2). Patients with a diagnosis of spontaneous urticaria were excluded (ICD-10 code L50). Four day windows around two- and four-weekly dosing schedules were employed.

To retain a higher degree of accuracy, approximately 29% of patients were excluded from the analyses for a number of reasons:

- Where dosing changed ≥3 times and patients were difficult to categorise.
- Where median dosing patterns fell outside of the licensed dose and frequency or the total number of patients was <6 and therefore anonymised.

To maintain patient confidentiality, counts of <6 were not reported. In these instances we assumed them to be '3'. When calculating the average annual cost, adherence was assumed to be 100%. In total of the 490 patients the analysis was conducted on 348 patients (approximately 71%). The results (see Table 117 calculated from Table 118) show that the average annual per patient cost for the years 2010-2014 is £11,370. This is equivalent to approximately 3.41 x 150mg vials every 4 weeks. Furthermore, the average annual per patient cost in this study for 2011, £7,959, is a close approximation of the £8,056 quoted in the NICE MTA[152,170]. Further still, the recent omalizumab HTA guidance from the National Centre for Pharmacoeconomics (NCPE, Ireland) reported the real world average annual cost of omalizumab to be approximately £11,723 (€15,824, value in sterling calculated using an exchange rate of 1EUR = 0.740845 GBP; 12 October 2015 [approximately 3.52x 150mg vials every 4 weeks]).[203] The NCPE review group concluded that higher doses are used in clinical practice leading to higher drug acquisition costs than those applied by the manufacturer. The review group therefore implemented 'real world' costs in additional analyses.[203]

Therefore the base case analysis applies an annual per patient omalizumab cost of £11,370 (=£872.22 / 4 weeks). A scenario analysis applies the annual cost assumed in the NICE MTA of omalizumab (£8,056 = £617.99 / 4 weeks). The ERG and Committee are asked to refer to the confidential addendum for comparison with add-on omalizumab with a GSK-assumed PAS price for omalizumab.

Table 117 Estimated annual per patient cost of adult severe persistent allergic asthma patients ≥18 years receiving treatment with omalizumab

Year	Estimated cost per patient per year	Estimated average 150mg vial usage per 4 weeks per patient
Total study average (2010-2014)	£11,370	3.41
2014	£12,027	3.61
2013	£10,632	3.19
2012	£10,097	3.03
2011	£7,959	2.39
2010	£9,858	2.96

Table 118 Dose and frequency of dose of omalizumab

	Total amount of mg dispensed							
Median days between vials	**75**	**150**	**225**	**300**	**375**	**450**	**525**	**600**
2 weeks			13 (4%)	39 (11%)	20 (6%)	26 (7%)	13 (4%)	18 (5%)
4 weeks	3 (1%)	52 (15%)	3 (1%)	84 (24%)		35 (10%)		42 (12%)

Estimated average cost of SoC

SoC was derived from MENSA and costed using BNF 2015.[202] A summary is provided in Table 119. Note that ICS and LABA were recorded in the trial as separates but have been costed to reflect clinical practice – use of combination ICS/LABA therapy as directed by the BTS/SIGN guidelines.[22]

Table 119: Standard of care use and costs

SoC	Users (MENSA)	Cost	Unit	Strength	Dose/day	Cost/cycle
ICS/LABA (weighted average, high dose)*	100%					£53.40
SABA (generic): Salbutamol	56.1%	£1.50	200	100mcg	800mcg	£0.94
Anti-leukotriene: Montelukast	49.7%	£2.42	28	10mg	10mg	£1.20
Theophyllines: Uniphyllin Continus	16.0%	£5.65	56	400mg	400mg	£0.45
OCS: prednisolone	24%	£1.33	28	5mg	12.5mg	£0.84
					Total	**56.84**

**Represents a weighted cost by high dose ICS/LABA use (Cegedim Strategic Data. Patient Data Report: Total Respiratory Market - Report 1 [GSK_1_001.DN2]. MAT June 2015-08-06) – see appendix 8.15*

5.5.3 Health-state unit costs and resource use

Routine appointments

Regardless of treatment option it is assumed severe asthma patients attend two consultant led out-patient attendances per year (£135.32/visit[196]), see Table 120. No differentiation is made between years. Therefore these costs will not impact the ICER. It is assumed that appointments for assessment of continuation of a biologic therapy will take place in one of the routine attendances. This is the same assumption made in the NICE MTA of omalizumab.[152,170]

Table 120 Annual routine appointment costs implemented in the economic evaluation

	SoC	Omalizumab	Mepolizumab
Frequency per year	2	2	2
Cost per year Unit cost £135.32[196] Service code: 340 Non-admitted face to face consultant-led follow up appointment	£270.64	£270.64	£270.64

Administration costs

It is assumed that all administrations for a biologic therapy are undertaken by a specialist asthma nurse, taking 10 minutes of time in total (£16.67, based on a per hour unit cost of £100[197]), see Table 121. This was confirmed at two separate advisory boards. This would include reconstitution time for mepolizumab. In the

NICE MTA of omalizumab an additional consultant-led outpatient attendance is included for patients initiated on omalizumab[170] which is not assumed in this economic evaluation. From clinician feedback a treatment decision to initiate on a biologic therapy would be made at one of the routine appointments and all administrations would be conducted by a specialist nurse. It is also assumed that patients on SoC may also be seen by a specialist nurse once per year for 10 minutes for example, for an adherence check-up.

The cost of conducting a routine full blood count to identify the persistent eosinophil threshold for potential eligible mepolizumab patients has not been included as this is currently conducted at routine attendances for severe asthma patients irrespective of whether they are started on mepolizumab or omalizumab. It should be noted that the cost for testing IgE levels for potentially eligible omalizumab patients has not been included however we understand that this is considerably more costly than a routine full blood count. A single RAST test alone is estimated to cost approximately £16.[204]

Table 121 Administration costs applied in the economic model

Unit cost: £100 (Specialist nurse /hour)[197]	**SoC**	**Cost per administration of biologic therapy**	
		Omalizumab	**Mepolizumab**
Cost per administration (10 mins)	£16.67 Assumes one per year (nurse check up)	£16.67*	£16.67

*Number of administrations per 28 week cycle is taken from the NICE MTA for omalizumab[152]; 1.43 per 28 days

Monitoring costs

For mepolizumab, it is assumed that patients will be monitored post-administration for one hour, as per the mepolizumab trial protocols. We assume this represents 15 mins of a specialist nurse time (i.e. £25[197] per one hour of monitoring). We assume that monitoring happens up to and including week 16, as per the NICE omalizumab appraisal.[170] Advisory feedback deemed this to be a reasonable assumption. At this time it should be noted there have been no cases of anaphylaxis for patients on mepolizumab.

For omalizumab we have incorporated the same assumptions used in the NICE MTA of omalizumab, monitoring requires 15 mins/hour of a specialist nurse time, up to and including week 16. It should be noted though that in the NICE MTA for omalizumab administrations 1-3 required 2 hours of monitoring (i.e. £50[197]), administrations in week 4-16 one hour of monitoring (£25[197]) respectively, see Table 122.

Table 122: Biologic monitoring costs implemented in the economic evaluation

Unit cost: £100 /hr[197] Specialist nurse time	**Monitoring cost per administration of biologic therapy**	
	Omalizumab	**Mepolizumab**
Unit cost for monitoring for administrations 1-3	£50	£25
Unit cost for monitoring for administrations up to 16 weeks	£25	£25

Exacerbation costs

Health care resource use associated with exacerbation resolution was collected for all DREAM and MENSA patients and included unscheduled GP consultations, outpatient appointments, emergency admissions hospital outpatient visits, ED visits, and hospital admissions. All patients in DREAM and MENSA (regardless of treatment group) experiencing clinically significant exacerbations were identified and the resource use within the days of the exacerbation were analysed to determine the rate of resource use per type of exacerbation. The resource consumption was used to estimate the resources by type of exacerbation, regardless of treatment group.

Table 123: Resource utilisation per exacerbation type (taken from DREAM and MENSA)

Resource	Type of exacerbation		
	OCS	ED	Hosp
Telephone call	0.554	0.258	0.708
Home day visit	0.018	0.000	0.047
Home night visit	0.004	0.000	0.000
Practice Visit	0.523	0.344	0.500
Outpatient attendance	0.072	0.118	0.066
Rescue OCS - total mg	350.0	491.1	758.7
Emergency room attendances	-	1.129	0.623
Hospitalisation	-	-	1.000

The use of OCS per type of exacerbation was determined by the GINA guidelines[205] and a Cochrane review[206], and is separated by use in the hospital/ED setting and after discharge. Table 124 presents the recommendation and the calculated total OCS dose.

Table 124: Recommended use and total OCS dose per exacerbation type

Resource	Recommendation	Total dose	Source
OCS burst	1 mg prednisolone/kg/day. max 50 mg/day, for 5-7 days	7*50 = 350 mg	GINA[205]
ED visit	ED: 125 mg per visit At discharge: 50 mg prednisolone/day, for 5-7 days	1.129*125 + 7*50 = 491 mg	Edmonds 2012[206] /MENSA/GINA
Hospitalisation	Hosp: 60 mg per day At discharge: 50 mg prednisone/day, for 5-7 days	6.81*60 + 7*50 = 759 mg	MENSA/GINA

Unit costs for resource use were obtained from NHS Reference costs 2013-14[196] or PSSRU[197]. Where necessary costs were updated to 2014 values using a UK-specific health service cost index (HCHS).

Table 125: Unit costs per resource for an exacerbation resolution

Resource	Cost	Source
Telephone call	£28.00	PSSRU 2014[197]
Home day visit	£46.00	PSSRU 2014[197]
Home night visit	£46.00	Assumption (conservative)
Practice Visit	£67.00	PSSRU 2014[197]
Outpatient attendance	£149.58	NHS reference costs 2013 to 2014[196]; Service code 340 Respiratory Medicine
OCS – prednisone per mg	£0.01	BNF 2015[202]
Emergency room attendances	£123.67	NHS reference costs 2013 to 2014[196];

		Emergency medicine
Hospitalisation	£1,277.59	NHS Reference costs 2012-13[196]; currency codes DZ15G, DZ15H, DZ15J, DZ15K, DZ15L

By summing the multiplied resource use and unit costs, the average cost of each type of exacerbation is: OCS burst; £65.73, ED visit; £192.26, Hospitalisation; £1,427.15

5.5.4 Miscellaneous unit costs and resource use

The economic evaluation takes an NHS perspective only. However we are aware that there are relevant PSS and other societal benefits that have not been included. Asthma UK reports that the impact of caring for someone with severe asthma is substantial, impacting on family relationships and difficulty in maintaining employment. As a result of providing both physical and emotional support, this can impact on a carer's well-being leading to anxiety and depression.[28] For patients, the extent of day-to-day symptoms can make it difficult to maintain previous full time employment and unlike other chronic conditions it can be more challenging for severe asthma patients to obtain a disability allowance.[28] Resultant financial stress can further negatively impact a patient's HRQL. In the ITT population of SIRIUS, percent work time missed due to health was 7.6% in the placebo group and 4.0% in the mepolizumab group.[51] These findings suggest that the resultant ICER may underestimate the true 'added' benefit of add-on mepolizumab in this severe refractory eosinophilic asthma population.

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

Table 126 tabulates all of the variables included in the economic evaluation.

i) Mepolizumab compared with standard of care

Table 126 Variables included in the economic evaluation and source

Variable		Mean	SE	Source	Distrib.	Lower	Upper
Exacerbation parameters (Section 5.3)							
Patient population: ITT							
Mepo: all pts	Rate	0.8771	0.08533	MENSA	Lognorm	0.72	1.06
SoC all pts	Rate	1.7439	0.09773	MENSA	Lognorm	1.56	1.94
Patients meeting mepo continuation criteria							
Exacerbations	Rate	0.5504	0.1459	MENSA	Lognorm	0.32	0.89
Proportion of patients meeting mepo continuation criteria							
Exacerbations	p%	0.91	0.015	MENSA	Beta	0.88	0.94
GSK proposed population excluding mOCS users with <4 exacerbations							
Mepo: all pts	Rate	1.2127	0.1482	MENSA	Lognorm	0.95	1.53
SoC all pts	Rate	3.1005	0.1795	MENSA	Lognorm	2.76	3.47
Patients meeting mepo continuation criteria							
Exacerbations	Rate	0.7232	0.2316	MENSA	Lognorm	0.37	1.27
Proportion of patients meeting mepo continuation criteria							
Exacerbations	p%	0.97	0.017	MENSA	Beta	0.93	0.99

GSK proposed population							
Mepo: all pts	Rate	1.2058	0.1271	MENSA	Lognorm	0.98	1.47
SoC all pts	Rate	2.650	0.157	MENSA	Lognorm	2.36	2.97
Patients meeting mepo continuation criteria							
Exacerbations	Rate	0.6447	0.2238	MENSA	Lognorm	0.31	1.18
Proportion of patients meeting mepo continuation criteria							
Exacerbations	p%	0.92	0.022	MENSA	Beta	0.87	0.96
Results of the NMA (for omalizumab comparison)							
Mepo: all pts	RR	0.496		NMA		0.41	0.60
Oma: all pts	RR	0.746		NMA		0.63	0.88
Additional clinical parameters omalizumab							
Oma: Meeting CC	ln(RR)	-0.99	0.167	INNOV	Norm	-1.31	-0.65
% meeting CC	p%	0.56	0.034	INNOV	Beta	0.50	0.63
Oma: all pts	ln(RR)	-0.56	0.159	EXALT	Norm	-0.87	-0.25
Oma: Meeting CC	ln(RR)	-0.89	0.146	EXALT	Norm	0.31	0.55
% meeting CC	p%	0.70	0.028	EXALT	Beta	0.65	0.75
Discontinuation							
Mepolizumab	p%	0.10	0.012	COSMOS	Beta	0.08	0.13
Omalizumab	p%	0.10	0.012	Assump	Beta	0.08	0.13
Asthma related mortality							
Watson 2007 + NRAD							
Exac OCS burst							
<12	p%	0.0001	NR	NRAD	NR	NR	NR
12 – 16	p%	0.0005	NR	NRAD	NR	NR	NR
17 – 44	p%	0.0006	NR	NRAD	NR	NR	NR
>45	p%	0.0038	NR	NRAD	NR	NR	NR
Exac ED visit							
<12	p%	0.0007	NR	NRAD	NR	NR	NR
12 – 16	p%	0.0023	NR	NRAD	NR	NR	NR
17 – 44	p%	0.0028	NR	NRAD	NR	NR	NR
>45	p%	0.0179	NR	NRAD	NR	NR	NR
Exac hospitalisation							
<12	p%	0.0010	0.000	Watson, 2007	Beta	0.000	0.002
12 – 16	p%	0.0032	0.001	Watson, 2007	Beta	0.001	0.007
17 – 44	p%	0.0038	0.001	Watson, 2007	Beta	0.003	0.005
>45	p%	0.0248	0.002	Watson, 2007	Beta	0.021	0.029
Watson 2007 (ScA – applied to hospitalised exacerbations only)							
<12	p%	0.0010	0.000	Watson, 2007	Beta	0.000	0.002
12 – 16	p%	0.0032	0.001	Watson, 2007	Beta	0.001	0.007
17 – 44	p%	0.0035	0.001	Watson, 2007	Beta	0.003	0.005
>45	p%	0.0248	0.002	Watson, 2007	Beta	0.021	0.029
Roberts 2013 (ScA – applied to hospitalised exacerbations only)							
18-24	p%	0.0015	0.000	Roberts	Beta	0.001	0.002
25-34	p%	0.0014	0.000	Roberts	Beta	0.001	0.002
35-44	p%	0.0020	0.000	Roberts	Beta	0.001	0.003
45-54	p%	0.0045	0.000	Roberts	Beta	0.004	0.005
55-64	p%	0.0127	0.001	Roberts	Beta	0.011	0.015
≥65	p%	0.0278	0.001	Roberts	Beta	0.026	0.030
Watson + De Vries +15% (approximated NICE approach TA 278)							
Applied to all Exac							

<12	p%	0.0007	NR	NICE TA 278	NR	NR	NR
12 – 16	p%	0.0022	NR	NICE TA 278	NR	NR	NR
17 – 44	p%	0.0027	NR	NICE TA 278	NR	NR	NR
>45	p%	0.0174	NR	NICE TA 278	NR	NR	NR
Watson + De Vries (approximated NICE approach TA 278 without + 15%)							
Applied to all Exac							
<12	p%	0.0006	NA	NICE TA 278	NR	NR	NR
12 – 16	p%	0.0019	NA	NICE TA 278	NR	NR	NR
17 – 44	p%	0.0023	NA	NICE TA 278	NR	NR	NR
>45	p%	0.0151	NA	NICE TA 278	NR	NR	NR
Utility values: SGRQ mapped to EQ-5D							
Patient population: ITT							
Mepo: all pts		0.796	0.01	MENSA	Beta	0.776	0.815
SoC all pts		0.738	0.015	MENSA	Beta	0.708	0.767
Patients meeting mepo continuation criteria							
Exacerbations		0.806	0.009	MENSA	Beta	0.788	0.823
GSK proposed population excluding mOCS users with <4 exacerbations							
Mepo: all pts		0.793	0.021	MENSA	Beta	0.750	0.833
SoC all pts		0.682	0.038	MENSA	Beta	0.605	0.754
Patients meeting mepo continuation criteria							
Exacerbations		0.805	0.018	MENSA	Beta	0.769	0.839
GSK proposed population							
Mepo: all pts		0.777	0.017	MENSA	Beta	0.743	0.809
SoC all pts		0.708	0.029	MENSA	Beta	0.650	0.763
Patients meeting mepo continuation criteria							
Exacerbations		0.795	0.016	MENSA	Beta	0.763	0.825
Utility values: EQ-5D (ScA)							
Patient population: Full ITT							
Mepo: all pts		0.802	0.005	DREAM	Beta	0.792	0.812
SoC all pts		0.794	0.005	DREAM	Beta	0.784	0.804
Patients meeting mepo continuation criteria							
Exacerbations		0.824	0.006	DREAM	Beta	0.812	0.836
GSK proposed population excluding mOCS users with <4 exacerbations							
Mepo: all pts		0.829	0.009	DREAM	Beta	0.811	0.846
SoC all pts		0.797	0.011	DREAM	Beta	0.775	0.818
Patients meeting mepo continuation criteria							
Exacerbations		0.834	0.012	DREAM	Beta	0.810	0.857
GSK proposed population							
Mepo: all pts		0.827	0.007	DREAM	Beta	0.813	0.841
SoC all pts		0.785	0.009	DREAM	Beta	0.767	0.802
Patients meeting mepo continuation criteria							
Exacerbations		0.837	0.009	DREAM	Beta	0.819	0.854
Utility decrement exacerbations							
OCS burst		-0.10	0.02	Lloyd	Beta	-0.064	-0.142
ED visit		-0.10	0.02	Assumption	Beta	-0.064	-0.142
Hospitalisation		-0.20	0.04	Lloyd	Beta	-0.128	-0.284

Duration: All	28	5.60	Lloyd	Gamma	18.120	39.995
Duration: OCS burst	12.68	0.549	MENSA (ScA)	Gamma	11.627	13.778
Duration: ED visit	10.41	1.23	MENSA (ScA)	Gamma	8.140	12.955
Duration: hospitalisation	20.70	3.27	MENSA (ScA)	Gamma	14.793	27.584
Treatment administration						
Cost Consultant (hour)	£135.32	£27.06	NHS Ref Costs	Gamma	£88	£193
Cost: Nurse (hour)	£100.00	£20.00	PSSRU	Gamma	£65	£143
Resource use exacerbations						
OCS burst						
Telephone call	0.55	0.03	DRE/MENS	Gamma	0.494	0.617
Home day visit	0.02	0.00	DRE/MENS	Gamma	0.009	0.029
Home night visit	0.00	0.00	DRE/MENS	Gamma	0.001	0.010
Practice Visit	0.52	0.03	DRE/MENS	Gamma	0.471	0.579
Outpatient attendance	0.07	0.01	DRE/MENS	Gamma	0.055	0.092
ED visit						
Telephone call	0.26	0.07	DRE/MENS	Gamma	0.133	0.424
Home day visit	0.00	0.00	DRE/MENS	Gamma	0.000	0.000
Home night visit	0.00	0.00	DRE/MENS	Gamma	0.000	0.000
Practice Visit	0.34	0.09	DRE/MENS	Gamma	0.195	0.535
Outpatient attendance	0.12	0.03	DRE/MENS	Gamma	0.062	0.193
A&E attendance	1.13	0.04	DRE/MENS	Gamma	1.050	1.211
Hospitalisation						
Telephone call	0.71	0.10	DRE/MENS	Gamma	0.523	0.919
Home day visit	0.05	0.02	DRE/MENS	Gamma	0.012	0.106
Home night visit	0.00	0.00	DRE/MENS	Gamma	0.000	0.000
Practice Visit	0.50	0.07	DRE/MENS	Gamma	0.370	0.649
Outpatient attendance	0.07	0.02	DRE/MENS	Gamma	0.027	0.121
A&E attendance	0.62	0.06	DRE/MENS	Gamma	0.512	0.744
Days in General Ward	6.17	0.53	DRE/MENS	Gamma	5.180	7.244
Days in Intensive care	0.64	0.29	DRE/MENS	Gamma	0.201	1.334
Unit costs Exacerbations						
Telephone call	£28.00	£5.60	PSSRU	Gamma	£18	£40
Home day visit	£46.00	£9.20	PSSRU	Gamma	£30	£66
Practice Visit	£67.00	£13.40	PSSRU	Gamma	£43	£96
Outpatient attendance	£149.58	£29.92	PSSRU	Gamma	£97	£214
A&E attendance	£123.67	£24.73	NHS	Gamma	£80	£177
Hospitalization	£1,277.59	£255.52	Spells	Gamma	£827	£1,825

ScA Scenario analysis

5.6.2 Assumptions

The key assumptions and their justification are detailed in the following tables. There is one area where we have chosen to deviate from the NICE reference case; by using SGRQ derived utility values from Phase III MENSA in the base case (Table 128). In a scenario analysis we explore the impact of using directly elicited EQ-5D values from Phase IIb DREAM. The rationale for not using these values in the basecase is provided in Section 5.4.1.

Table 127: Key model assumptions: structural and treatment effects

Assumption	Justification	Source
Data from multi-country trials is applicable to UK	Consistent with established economic models	Norman 2013[152] Faria 2014[159]

Clinically significant exacerbation rates (32 weeks) by treatment group can be annualised	Consistent with established economic models	Norman 2013[152] Faria 2014[159]
Constant exacerbation rates for SoC and biologic add-on therapy throughout time	Consistent with established economic models	Norman 2013[152] Faria 2014[159]
Exacerbation are classified into three categories defined by the resource incurred	In line with endpoints defined in the mepolizumab clinical trial programme	MENSA / DREAM / SIRIUS
Patients are at risk of asthma related mortality as a result of an exacerbation	Relevant data for mortality risk of hospitalised exacerbations is identified in the systematic literature search. Non-hospitalised mortality risk is estimated from the NRAD report (identified through hand searching).	Watson 2007[167] NRAD[49]
After determination of response, biologic treatment cohorts are divided into patients meeting and not meeting continuation criteria as part of a continuation review.	Aligns to anticipated SmPC for mepolizumab and SmPC and current clinical practice for omalizumab. Differences in exacerbations and quality of life observed between the patient groups in the clinical trials are appropriately applied in the economic model	Mepolizumab draft SmPC[15] Omalizumab SmPC[138] NHSE Severe asthma service specification[17]
Patients meeting continuation criteria maintain their response as long as they remain on treatment.	Consistent with established economic models	Norman 2013[152] Faria 2014[159]
Patients not meeting continuation criteria revert to SoC for the remaining time	Consistent with established economic models	Norman 2013[152] Faria 2014[159]
Time point of the assessment of mepolizumab treatment continuation is assumed at week 52	Aligns to anticipated SmPC for mepolizumab.	Mepolizumab draft SmPC[15]
Biologic treatment duration was assumed to be 10 years	Consistent with established economic models; agreement from clinical feedback	Norman 2013[152] Faria 2014[159]
The model structure allows for inclusion of biologic treatment withdrawal.	To reflect that in clinical practice patients may discontinue treatment for various reasons beyond the point at which a continuation review is conducted.	DREAM, MENSA, SIRIUS and COSMOS
The impact of adverse drug reactions is not considered.	Incidence of AEs were relatively consistent across both SoC alone and mepolizumab arms. Consistent with established economic models.	DREAM, MENSA, SIRIUS Norman 2013[152] Faria 2014[159]

Table 128: Key model assumptions: HRQL & Costs

Assumption	Justification	Source
All-cause mortality was not adjusted for asthma-related mortality	Minimal impact on the results due to low mortality associated with asthma	-
Health status of daily asthma symptoms are based on the SGRQ data, collected in the MENSA trial, mapped to EQ-5D	EQ-5D was not sensitive to changes in a severe asthma population (DREAM, Phase IIb). EQ-5D was not captured in phase III trials.	MENSA
HRQL data for asthma symptom health states for mepolizumab were applied to	Absence of comparative data to inform an indirect comparison.	-

omalizumab		
Exacerbations are associated with lower HRQL, independent of treatment	Consistent with established economic models and HRQL literature	Lloyd 2007[165] Norman 2013
Utility decrement of ED visit is same as OCS burst	Conservative approach in absence of appropriate data	-
HRQL loss associated with an exacerbation assumed to last 4 weeks, corresponding to the follow-up period of 4 weeks (from Lloyd 2007)	Consistent with the source for which the utility decrement is taken from and previous economic model approaches.	Lloyd 2007[165] Norman 2013[152] Faria 2014[159]
All administrations of a biologic are given by a specialist nurse, taking 10 minutes to complete	Clinician feedback; based on current clinical practice for the administration of omalizumab	Norman 2013[152] Faria 2014[159]
For biologic treatment all patients are monitored by a specialist nurse up to 16 weeks.	Consistent with previous economic approach and deemed reasonable by clinician feedback	Norman 2013[152]
For patients on mepolizumab, monitoring is assumed to take one hour costed at 15 mins / hour	Consistent with the trial protocols for mepolizumab and in agreement with clinical feedback	DREAM, MENSA, SIRIUS
For patients on omalizumab, monitoring is assumed to take two hours costed at 15 mins / hour, for the first three administrations and one hour thereafter up to week 16,	Consistent with established economic models	Norman 2013[152]
For all treatments including SoC, patients are expected to have two routine appointments per year in an outpatient setting, consultant led. Additionally, patients on SoC are expected to have one specialist nurse appointment per year (medication / adherence check).	Deemed a reasonable approach from advisory board clinician feedback	-
Resource utilisation to treat exacerbations obtained from DREAM and MENSA	Resource is matched to the type of exacerbation and extracted from DREAM and MENSA; deemed a reasonable approach from advisory board clinician feedback	DREAM, MENSA

5.7 Base-case results

In the main submission the following cost-effectiveness analyses are presented:

- Mepolizumab PAS price versus SoC alone in all populations (ITT, GSK proposed population excluding mOCS users with <4 exacerbations and GSK proposed population)
- Mepolizumab PAS price versus List price for omalizumab in the ITT population.

The ERG and NICE Committee are asked to refer to the confidential addendum to this submission for the following cost-effectiveness analyses:

- Mepolizumab PAS price versus PAS price for omalizumab (GSK-estimated) in the ITT population.

5.7.1 Summary of the link between the clinical and cost-effectiveness results

Table 129 summarises the model inputs compared with the clinical data for the interventions and comparators

Table 129 Summary of model results compared with clinical data

	SoC		Mepolizumab		Omalizumab	
	Clinical trial result	**Model Input****	**Clinical trial result**	**Model Input****	**Clinical trial result**	**Model Input**
Population: ITT						
Exacerbation rates /yr [MENSA] Section 5.3.2						
Pre-continuation review	1.75 (Not defined by pre- and post-continuation) [section 4.7.5.1]	1.744	0.81 (Not defined by pre- and post-continuation; 100mg SC) [section 4.7.5.1]	0.877 (direct evidence) 0.496 (NMA)	0.7474[152]	0.746
Post-continuation review		NA		0.550 (direct evidence) 0.316 (NMA)	0.373[152]	0.373
Utility – SGRQ derived EQ-5D values[MENSA] Section 5.4.5						
Pre-continuation review	SGRQ reported; LS mean (SE) 37.7 (1.16) [section 4.7.5.3]	0.738	SGRQ reported; LS mean (SE) 30.7 (1.13) [section 4.7.5.3]	0.796	NA	NA
Post-continuation review		NA		0.806	NA	NA
Utility – EQ-5D values (Scenario analysis)[DREAM] Section 5.4.5						
Pre-continuation review	EQ-5D index score 52 wks; mean (SE) 0.82 (0.214) Summarised in section 4.7.5 and provided in CSR	0.794	EQ-5D index score 52 wks 75mg IV; mean (SE) 0.81 (0.209) Summarised in section 4.7.5 and provided in CSR	0.802	NA	NA
Post-continuation review		NA		0.824	NA	NA
GSK proposed population excluding mOCS users with <4 exacerbations						
Exacerbation rates /year [MENSA] Section 5.3.2						
Pre-continuation review	3.10 (Not defined by pre- and post-continuation) [section 4.7.4.1]	3.101	1.22 (Not defined by pre- and post-continuation; 100mg SC only) [section 4.7.4.1]	1.213	NA	NA
Post-continuation review		NA		0.723	NA	NA
Utility – SGRQ derived EQ-5D values [MENSA] Section 5.4.5						
Pre-continuation review	SGRQ reported; LS mean (SE) 42.4 (2.64) [section 4.7.4.3]	0.682	SGRQ reported; LS mean (SE) 29.5 (2.32) [section 4.7.4.3]	0.793	NA	NA
Post-continuation review		NA		0.805	NA	NA
Utility – EQ-5D values (Scenario analysis)[DREAM] Section 5.4.5						
Pre-continuation		0.797		0.829	NA	NA

review						
Post-continuation review		NA		0.834	NA	NA
GSK proposed population						
Exacerbation rates /year [MENSA] Section 5.3.2						
Pre-continuation review	2.65 (Not defined by pre- and post-continuation) [section 4.7.4.1]	2.650	1.32 (Not defined by pre- and post-continuation; 100mg SC only) [section 4.7.4.1]	1.206	NA	NA
Post-continuation review		NA		0.645	NA	NA
Utility – SGRQ derived EQ-5D values [MENSA] Section 5.4.5						
Pre-continuation review	SGRQ reported; LS mean (SE) 41.3 (2.08) [section 4.7.4.3]	0.708	SGRQ reported; LS mean (SE) 31.3 (1.86) [section 4.7.4.3]	0.777	NA	NA
Post-continuation review		NA		0.795	NA	NA
Utility – EQ-5D values (Scenario analysis)[DREAM] Section 5.4.5						
Pre-continuation review		0.785		0.827	NA	NA
Post-continuation review		NA		0.837	NA	NA

** The economic model pools both the 75mg IV and 100mg SC mepolizumab arms

Values implemented in the economic model differ from those in the clinical sections. This is due to the pooling of the 75mg IV and 100mg SC mepolizumab arms from MENSA. Distribution of exacerbations, type and frequency of resource use for exacerbation resolution implemented in the economic evaluation is not reported in the clinical sections of this submission but are derived from MENSA or MENSA and DREAM respectively (see Table 105 and Table 123).

5.7.2 Markov trace

Please refer to the model (worksheet 'Model Engine') for the Markov trace by treatment (SoC, mepolizumab or omalizumab)

5.7.3 Base-case incremental cost effectiveness analysis results

Base case pair-wise and incremental analyses for mepolizumab versus SoC alone and mepolizumab versus list price omalizumab are presented below.

Table 130 shows that the cost-effectiveness of add-on mepolizumab (+PAS) compared with SoC alone is £19,526/QALY gained in the GSK proposed population and £15,394/QALY gained in the GSK proposed population excluding mOCS users with <4 exacerbations. Mepolizumab provides an additional [redacted] QALYs at an additional cost of [redacted] in the GSK proposed population and [redacted] QALYs at an additional cost of [redacted] in the GSK proposed population excluding mOCS users with <4 exacerbations. Table 131 shows that add-on mepolizumab is dominant versus add-on omalizumab with QALY gains of [redacted] and cost savings of [redacted] in the ITT population (as measured by the NMA). However given that this value does not include the PAS price of omalizumab this does not provide a realistic estimate of the cost-effectiveness compared with omalizumab for the NHS. This is estimated in the confidential addendum.

Table 130 Add-on Mepolizumab versus SoC alone; by population (based on MENSA)

A. Pairwise analysis

	Full ITT			GSK proposed population excluding mOCS with <4 exacerbations			GSK proposed population		
	Mepo	**SoC**	**Mepo vs. SoC**	**Mepo**	**SoC**	**Mepo vs. SoC**	**Mepo**	**SoC**	**Mepo vs. SoC**
Effectiveness (undiscounted)									
Life years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs									
QALYs Markov health states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY decrement exacerbations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Effectiveness (discounted)									
Life years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs									
QALYs Markov health states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY decrement exacerbations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs (discounted)									
Intervention costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: OCS burst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: ED visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: Hospital	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness									
Cost per QALY gained			**£31,659**			**£15,394**			**£19,526**

B. Incremental analyses

Technologies	Total costs £	Total LYG	Total QALYs	Incremental costs £	Incremental LYG	Incremental QALYs	ICER (£) versus baseline QALYs	ICER (£) incremental (QALYs)
Patient population: Full ITT								
Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	**£31,659**
GSK proposed population excluding mOCS users with <4 exacerbations								
Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	**£15,394**
GSK proposed population								
Mepolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	**£19,526**

Table 131 Add-on Mepolizumab versus omalizumab alone and versus SoC alone; Full ITT (indirect evidence)

A. Pairwise analysis

	Full ITT				
	Mepo	***Omalizumab***	***Mepo vs. omalizumab***	***SoC alone***	***Mepo vs. SoC alone***
Effectiveness (undiscounted)					
Life years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs					
QALYs Markov health states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY decrement exacerbations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Effectiveness (discounted)					
Life years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs					
QALYs Markov health states	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY decrement exacerbations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs (discounted)					
Intervention costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: OCS burst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: ED visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: Hospital	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost-effectiveness					
Cost per QALY gained			**Dominant**		**£31,618**

B. Incremental analyses

Technologies	Total costs £	Total LYG	Total QALYs	Incremental costs £	Incremental LYG	Incremental QALYs	ICER (£) versus baseline QALYs	ICER (£) incremental (QALYs)
Patient population: Full ITT								
SoC	[redacted]	[redacted]	[redacted]					
Omalizumab (LIST)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£76,893**	**£76,893**
Mepolizumab (+PAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£31,618**	**Dominant**

5.7.4 Expected LYG and QALYs by health state for intervention and comparators

Expected LYG and QALYs by health state are provided in Table 132 and Table 133.

i) Mepolizumab (+PAS) versus SoC alone

Table 132 Expected LYG and QALYs by health state for mepolizumab and SoC, by patient population (direct evidence)

	Full ITT		GSK proposed population excl. mOCS with <4 exac		GSK proposed population	
	SoC+ Mepolizumab	SoC	SoC+ Mepolizumab	SoC	SoC+ Mepolizumab	SoC
LYs						
All/Responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Continuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs						
All/Responders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Continuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exac: OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exac: ED visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exac: Hosp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ii) Mepolizumab (+PAS) versus omalizumab (LIST) and SoC alone (NMA derived)

Table 133 Expected LYG and QALYs by health state for mepolizumab and omalizumab, Full ITT (indirect evidence)

	Full ITT		
	SoC+ mepolizumab	SoC + omalizumab	SoC alone
LYs			
All/Responders	[redacted]	[redacted]	[redacted]
Continuations	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
QALYs			
All/Responders	[redacted]	[redacted]	[redacted]
Continuations	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]
Exac: OCS	[redacted]	[redacted]	[redacted]
Exac: ED visit	[redacted]	[redacted]	[redacted]

Exac: Hosp	[redacted]	[redacted]	[redacted]	
Total	[redacted]	[redacted]	[redacted]	

5.7.5 Disaggregated incremental QALYs

Disaggregated incremental QALYs are shown in Table 134 to Table 136.

i) Mepolizumab (+PAS) versus SoC alone

Table 134 Incremental QALYs by health state, Add-on mepolizumab versus SoC, all populations (direct evidence)

Health state	QALY Mepo + SoC	QALY SoC alone	Increment	Absolute increment	% absolute increment
Patient population: Full ITT					
All / meeting Continuation review	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not meeting Continuation review	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: eD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: Hosp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GSK proposed population excl. mOCS and <4 exacerbations					
All / meeting Continuation review	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not meeting Continuation review	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: eD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: Hosp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GSK proposed population					
All / meeting Continuation review	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not meeting Continuation review	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: eD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: Hosp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

eD Emergency Department visit

iia) Mepolizumab (+PAS) versus omalizumab (LIST) (NMA derived)

Table 135 Incremental QALYs by health state, Add-on mepolizumab versus add-on omalizumab, full ITT (indirect evidence)

Health state	QALY Mepo + SoC	QALY Oma + SoC	Increment	Absolute increment	% absolute increment
Patient population: Full ITT					
All / meeting Continuation review	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not meeting Continuation review	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: eD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: Hosp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

eD Emergency Department Visit

iib) Mepolizumab (+PAS) versus SoC alone (NMA derived)

Table 136 Incremental QALYs by health state, Add-on mepolizumab versus SoC, full ITT (indirect evidence)

Health state	QALY Mepo + SoC	QALY SoC	Increment	Absolute increment	% absolute increment
Patient population: Full ITT					
All / meeting Continuation review	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not meeting Continuation review	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: eD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: Hosp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

eD Emergency Department visit

5.7.6 Disaggregated incremental costs

Disaggregated costs are provided in Table 137 to Table 139.

i) Mepolizumab (+PAS) versus SoC alone

Table 137 Incremental costs by health state, Add-on mepolizumab versus SoC, all populations (direct evidence)

Health state	Costs Mepo + SoC	Costs SoC alone	Increment	Absolute increment	% absolute increment
Patient population: Full ITT					
All / meeting Continuation review	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not meeting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Continuation review					
Discontinuations					
Exa: OCS					
Exa: eD					
Exa: Hosp					
Total					
GSK proposed population excluding mOCS users with <4 exacerbations					
All / meeting Continuation review					
Not meeting Continuation review					
Discontinuations					
Exa: OCS					
Exa: eD					
Exa: Hosp					
Total					
GSK proposed population					
All / meeting Continuation review					
Not meeting Continuation review					
Discontinuations					
Exa: OCS					
Exa: eD					
Exa: Hosp					
Total					

eD Emergency Department visit

iia) Mepolizumab (+PAS) versus omalizumab (LIST) (NMA derived)

Table 138 Incremental Costs by health state, Add-on mepolizumab versus add-on omalizumab, full ITT (indirect evidence)

Health state	Costs Mepo + SoC	Costs Oma + SoC	Increment	Absolute increment	% absolute increment
Patient population: Full ITT					
All / meeting Continuation review					
Not meeting Continuation review					
Discontinuations					
Exa: OCS					
Exa: eD					
Exa: Hosp					
Total					

eD Emergency Department visit

iib) Mepolizumab (+PAS) versus SoC alone (NMA derived)

Table 139 Incremental Costs by health state, Add-on mepolizumab versus SoC alone, full ITT (indirect evidence)

Health state	Costs Mepo + SoC	Costs SoC	Increment	Absolute increment	% absolute increment
Patient population: Full ITT					
All / meeting Continuation review	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not meeting Continuation review	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: eD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exa: Hosp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

eD Emergency Department visit

5.7.7 Predicted resource use by category of cost

Predicted resource use by category of cost is provided in Table 140 to Table 142.

i) Mepolizumab (+PAS) versus SoC alone

Table 140 Predicted resource use by category of cost, Add-on mepolizumab versus SoC, all populations (direct evidence)

Health state	Costs Mepo + SoC	Costs SoC alone	Increment	Absolute increment	% absolute increment
Patient population: Full ITT					
Intervention costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: OCS burst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: ED visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: Hospital	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OCS related AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GSK proposed population excluding mOCS users with <4 exacerbations					
Intervention costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: OCS burst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation: ED visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: Hospital	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OCS related AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GSK proposed population					
Intervention costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: OCS burst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: ED visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: Hospital	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OCS related AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ED Emergency Department visit

iia) Mepolizumab (+PAS) versus omalizumab (LIST) and SoC alone (NMA derived)

Table 141 Predicted resource use by category of cost, Add-on mepolizumab versus add-on omalizumab, full ITT (indirect evidence)

Health state	Costs Mepo + SoC	Costs Oma + SoC	Increment	Absolute increment	% absolute increment
Patient population: Full ITT					
Intervention costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: OCS burst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: ED visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: Hospital	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OCS related AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

iib) Mepolizumab (+PAS) versus SoC alone (NMA derived)

Table 142 Predicted resource use by category of cost, Add-on mepolizumab versus SoC, full ITT (indirect evidence)

Health state	Costs Mepo + SoC	Costs SoC	Increment	Absolute increment	% absolute increment
Patient population: Full ITT					
Intervention costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: OCS burst	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: ED visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exacerbation: Hospital	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OCS related AE costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

Multivariate probabilistic sensitivity analysis was conducted. In total, 2000 simulations were processed to represent the uncertainty of model results by varying all parameters simultaneously, taking random draws from their assumed distributions. For the outputs of the network meta-analysis, 2000 simulations were directly extracted from the WinBugs code.

Table 143 shows the additional parameters that were varied in the PSA that could not be included in the deterministic univariate sensitivity analyses because of their interdependencies. The applied Dirichlet distribution is a probability distribution over the space of multinomial distributions. The distribution is suited here as the sum of the three individual components should always be equal one. All other parameters and distributions are described in Table 126.

Table 143: Additional parameters in the multivariate probabilistic sensitivity analysis (example for the MENSA full trial population)

Variable	Mean	SE	Source	Distribution
Proportion of each subtype of clinically significant exacerbations				
Exacerbation: OCS burst	83.1%	0.018	MENSA	Dirichlet
Exacerbation: ED visit	8.7%	0.013	MENSA	Dirichlet
Exacerbation: Hospitalization	8.2%	0.013	MENSA	Dirichlet

Results of the PSA derived ICERs

i) Mepolizumab versus SoC alone (MENSA)

The results of the PSA derived ICERs for the comparison of mepolizumab versus SoC alone (Table 144) are not dissimilar from the deterministic ICERs reported in Section 5.7.3 for the ITT and GSK proposed populations.

Table 144 Results of the PSA derived ICERs (direct evidence)

	Total costs		Total QALYs		∆ Costs	∆ QALYs	ICER
	Mepo	SoC	Mepo	SoC	Vs. SoC	Vs. SoC	
Patient population: Full ITT (direct evidence)							
Deterministic							
PSA							**£31,692**
L 95% CI							
U 95% CI							
GSK proposed population excluding mOCS users with <4 exacerbations							
Deterministic							
PSA							**£15,478**
L 95% CI							
U 95% CI							
GSK proposed population							
Deterministic							
PSA							**£19,511**
L 95% CI							
U 95% CI							

Scatter plots and CEACs for the GSK proposed populations are presented below. A Scatter plot and CEAC for the ITT population is provided in Appendix 8.17. Figure 27 shows that in the GSK proposed population excluding mOCS users with <4 exacerbations the incremental QALYs range from approximately [redacted] to [redacted] and incremental costs from [redacted] to [redacted]. Figure 28 shows that the probability that mepolizumab is cost-effective at a willingness to pay of approximately £15,000 / QALY gained is 50% rising to 100% with an increase in the threshold to £30,000 / QALY gained.

Figure 29 shows the GSK proposed population, and versus SoC alone mepolizumab offers incremental QALYs of [redacted] to [redacted] and incremental costs of [redacted] to [redacted]. The CEAC in

Figure **30** shows that at a willingness to pay of approximately £20,000 the probability that mepolizumab is a cost-effective alternative is 50% rising to >95% at a willingness to pay of £30,000/QALY gained.

Figure 27 Plot of the incremental costs and QALYs for mepolizumab versus SoC alone; GSK proposed population excluding mOCS users with <4 exacerbations

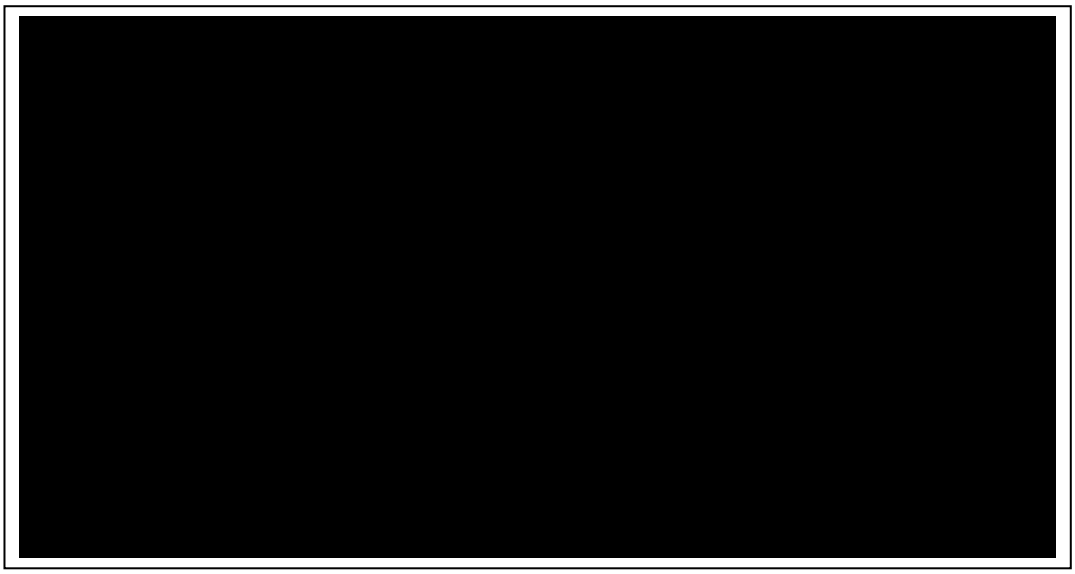


Figure 28 Acceptability curve for pairwise comparison of mepolizumab versus SoC alone; GSK proposed population excluding mOCS users with <4 exacerbations

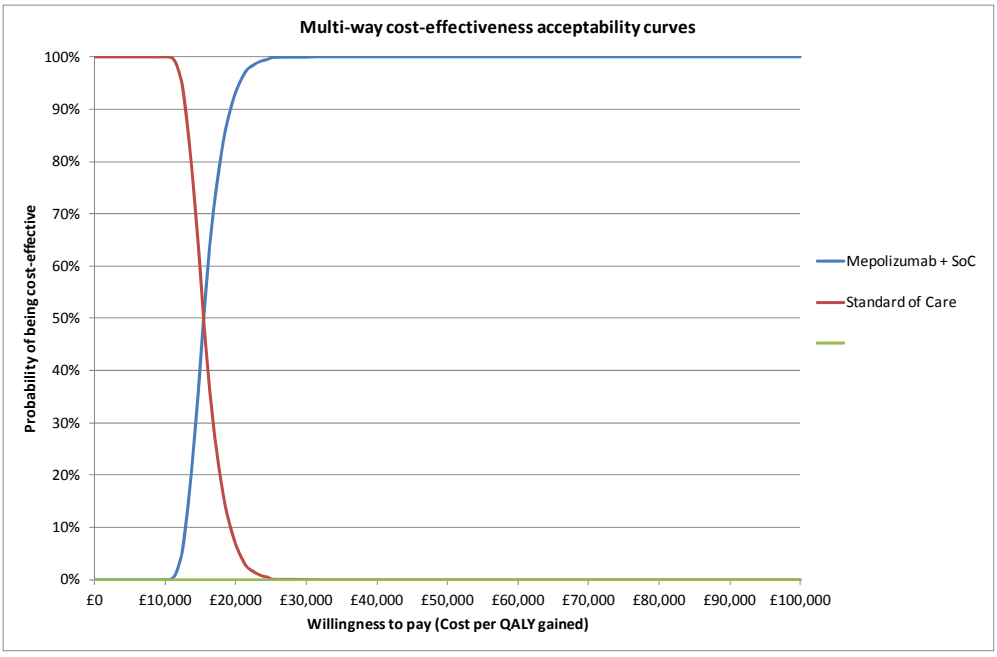


Figure 29 Plot of the incremental costs and QALYs for mepolizumab versus SoC alone; GSK proposed population

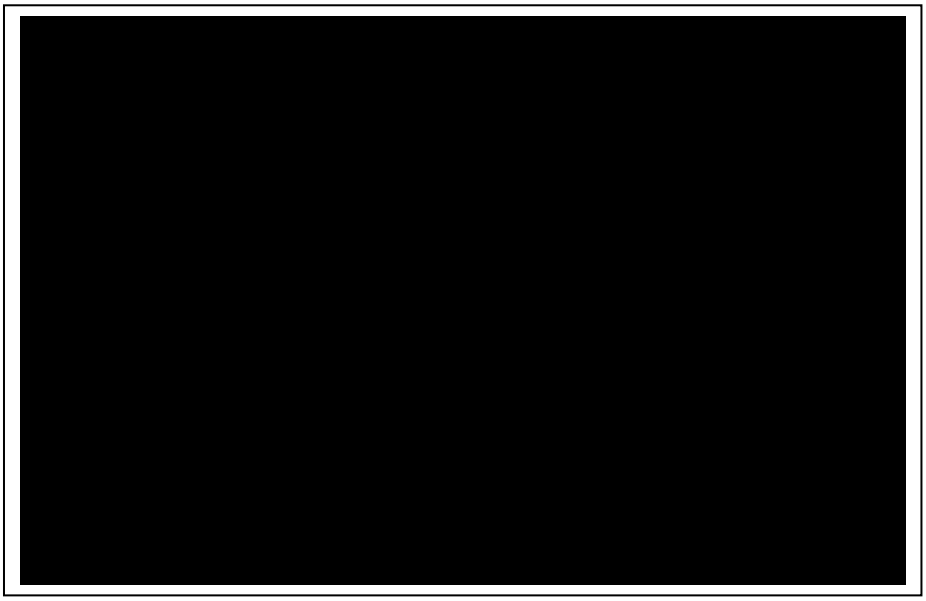
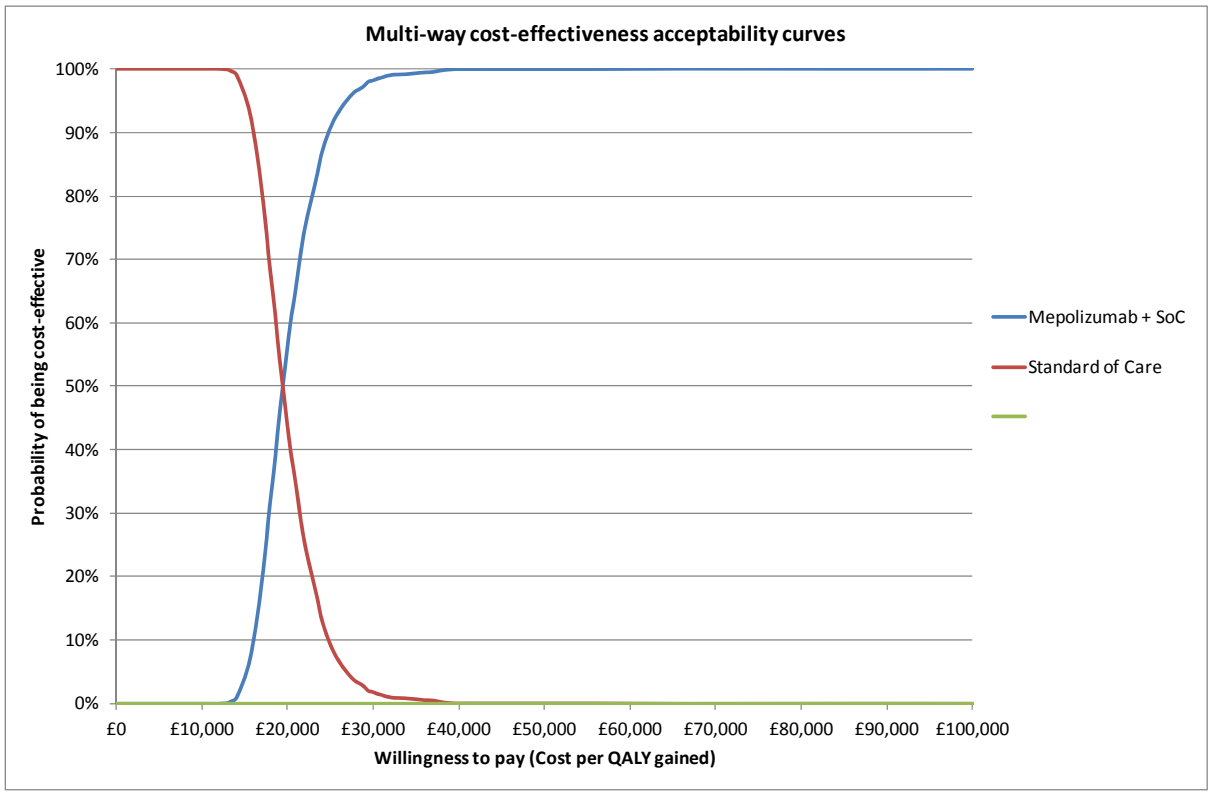


Figure 30 Acceptability curve for pairwise comparison of mepolizumab versus SoC alone; GSK proposed population



ii) Mepolizumab (+PAS) versus omalizumab and SoC alone (NMA derived)

The PSA of mepolizumab versus omalizumab and SoC (in the full trial populations due to limitations in the evidence informing the NMA) generated ICERs similar to the deterministic ICERs in Section 5.7.3. Table 145 shows that the ICER versus SoC alone is £31,672 / QALY gained and Dominant versus omalizumab. The Committee are asked to refer to the confidential addendum for ICERs based on both the PAS for mepolizumab and the assumed PAS for omalizumab. The Scatter plot in Figure 31 for comparison versus SoC alone is not dissimilar from the Scatter plot versus SoC where data is derived from MENSA only. Comparing mepolizumab to omalizumab, the scatter plot shows incremental QALYs ranging from [redacted] to [redacted]. However this must be interpreted in light of the limitations of the evidence available in the NMA. Mepolizumab also shows cost savings versus omalizumab in this comparison but again the Committee are asked to refer to the confidential appendix for application of an assumed PAS for omalizumab.

Table 145 Results of the PSA derived ICERs; mepolizumab versus omalizumab and SoC alone (indirect evidence)

	Total costs			Total QALYs			Δ Costs		Δ QALYs		ICER	
	Mepo	Oma	Soc	Mepo	Oma	Soc	Vs. Oma	Vs. SoC	Vs. Oma	Vs. SoC	Vs. Oma	Vs. SoC
Patient population: Full ITT												
Deterministic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]						
PSA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**	**£31,672**
L 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
U 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

Figure 31 Plot of the incremental costs and QALYs for mepolizumab versus SoC alone and versus omalizumab alone; Full ITT (indirect evidence)

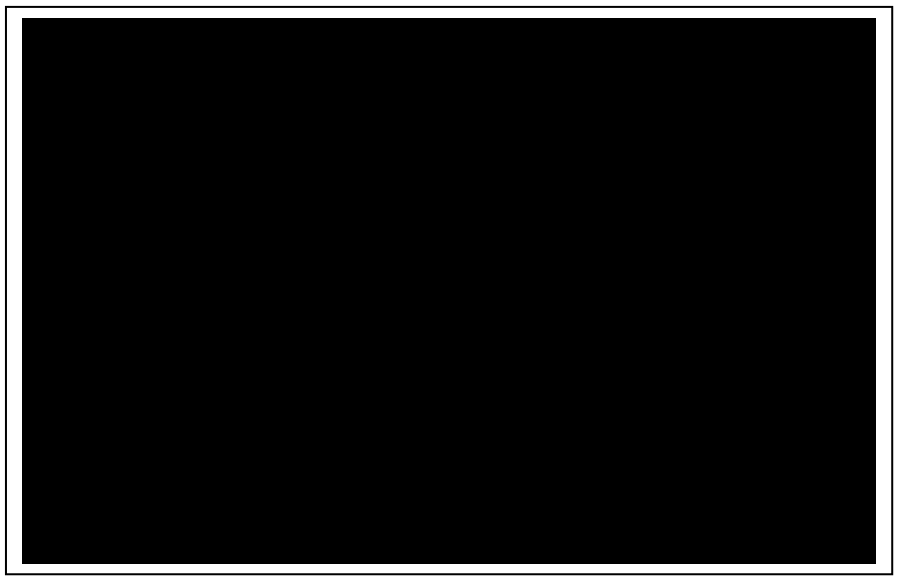
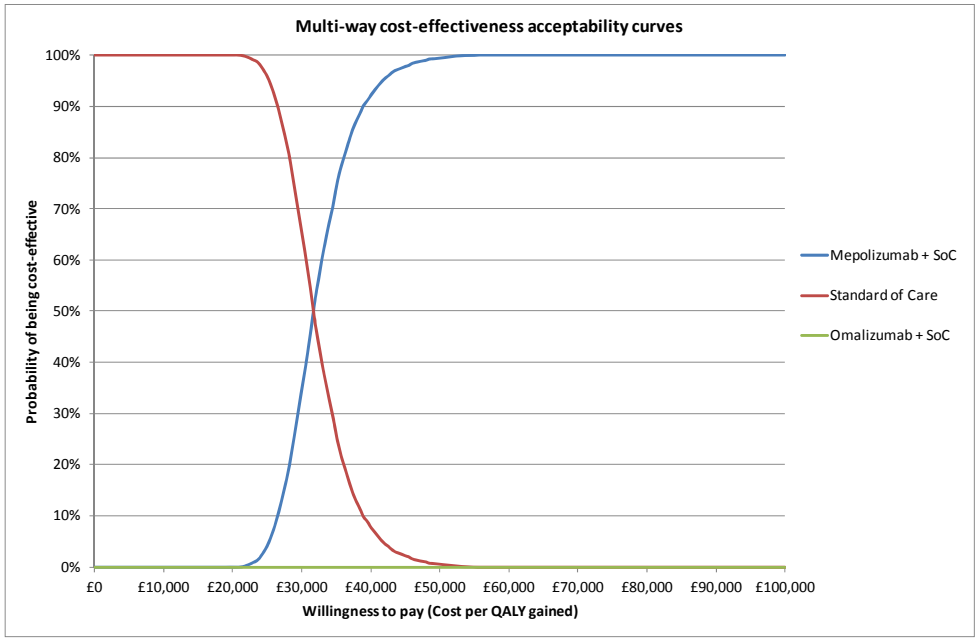


Figure 32 Acceptability curve for pairwise comparison of mepolizumab versus omalizumab alone; Full ITT



5.8.2 Deterministic sensitivity analysis

Within the deterministic univariate sensitivity analyses, the impact on incremental QALYs and costs was determined when each model parameter was varied separately within the limits of its 95% confidence interval. The parameters, their distributions and outer limits are provided in Table 126. The results of the analyses

are presented in tornado graphs (10 most sensitive model parameters). The tornado graphs for the ITT analysis (based on MENSA) is provided in Appendix 8.17.

i) Mepolizumab (+PAS) versus SoC alone (MENSA)

Figure 33 ICER mepolizumab versus SoC alone; GSK proposed population excluding mOCS users with <4 exacerbations

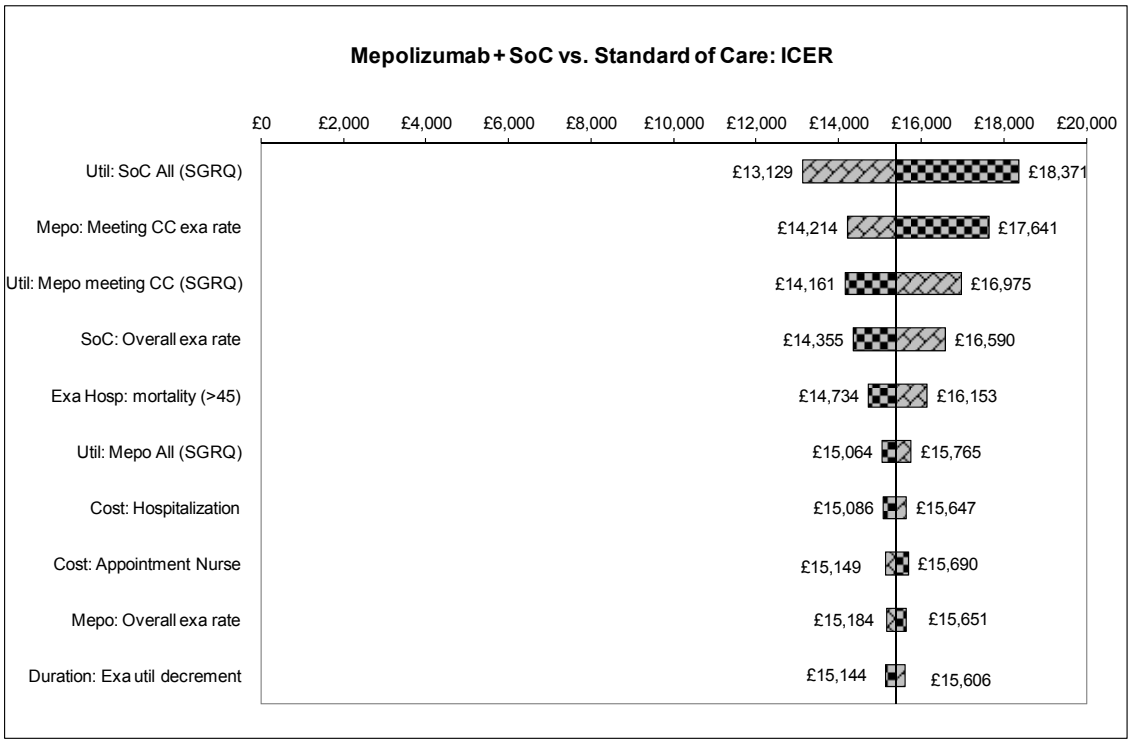
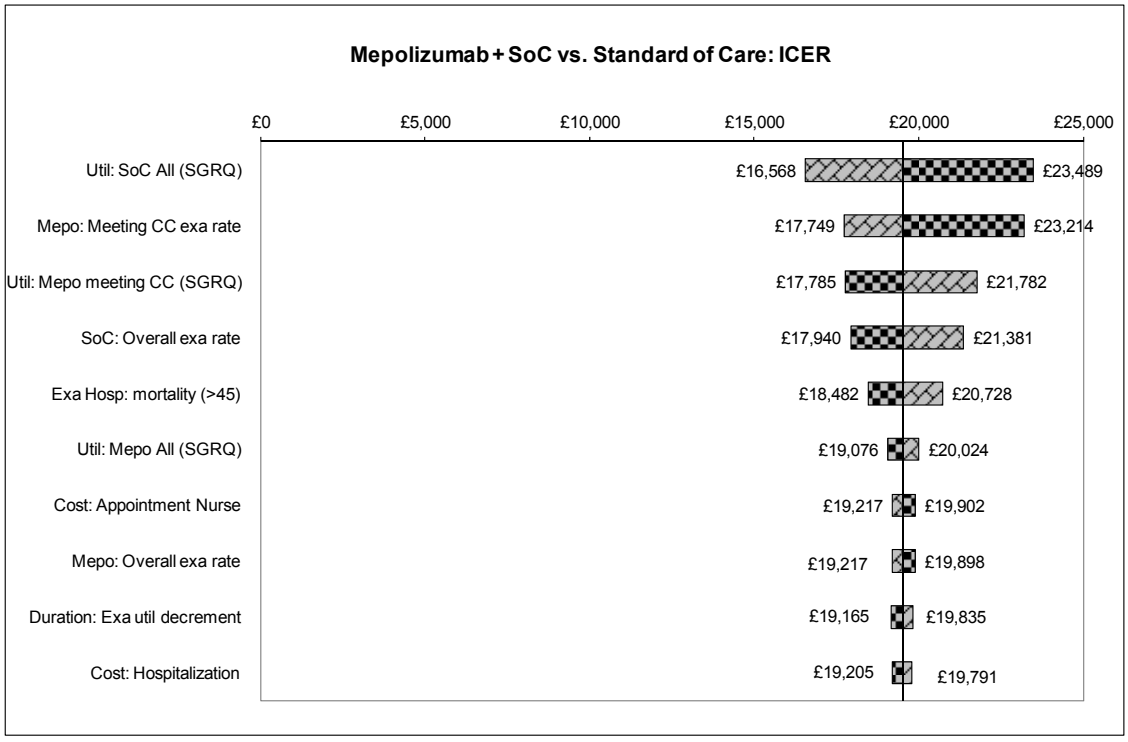


Figure 34 ICER mepolizumab versus SoC alone; GSK proposed population

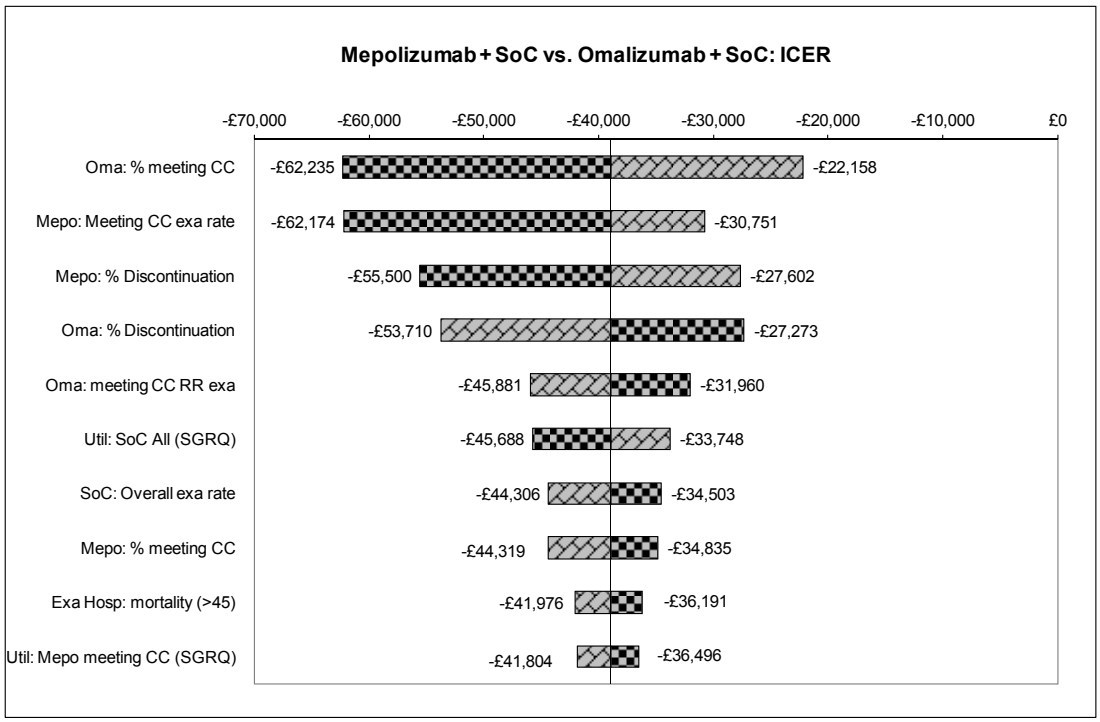


The tornado graphs in Figure 33 and Figure 34 for the GSK proposed populations show that the top six parameters which the ICER is most sensitive include: the SGRQ derived utility applied to the SoC arm, the proportion of mepolizumab meeting the continuation criteria, the SQRQ derived utility applied to patients meeting the mepolizumab continuation criteria, overall exacerbation rates, mortality (exacerbations resulting in a hospitalisation) and SGRQ derived utility assumed for patients on mepolizumab. However the resulting ICERs for each particular sensitive parameter still falls below £30,000/QALY gained.

iia) Mepolizumab (+PAS) versus omalizumab (NMA derived)

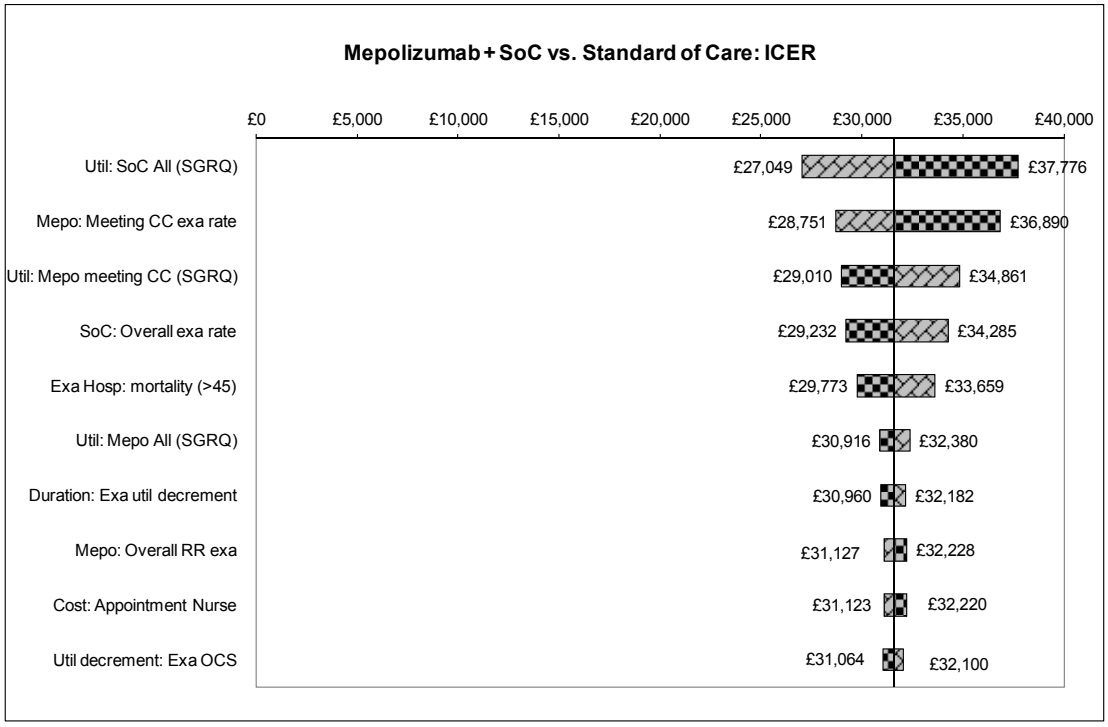
The univariate sensitivity analyses were also conducted versus omalizumab and SoC (based on indirect evidence). Versus SoC (Figure 36) alone sensitive parameters were the same as outlined above for a comparison derived from MENSA only. For comparison versus omalizumab as shown in Figure 35 (in the context that this comparison uses the list price of omalizumab) the most sensitive parameters include: proportion of omalizumab patients meeting the continuation criteria, assumed biologic discontinuations year on year, the revised biologic exacerbation rate post continuation, and SGRQ derived utility for the SoC arm. Again all resultant ICERs for each of the sensitive parameters do not exceed £30,000 / QALY gained.

Figure 35 ICER mepolizumab versus omalizumab; Full ITT (indirect evidence)



iib) Mepolizumab (+PAS) versus SoC alone (NMA derived)

Figure 36 ICER mepolizumab versus SoC alone; Full ITT (indirect evidence)



5.8.3 Scenario analysis

Several relevant scenario analyses have been conducted to explore the sensitivity of the economic results to key structural and data assumptions used in the model. All scenario analyses are summarised in the table below and results are shown below that.

Table 146 Summary of base case and scenario analyses

Parameter	Base case analysis	Alternative scenarios
Patient age	50.1 years	30; 65
Treatment duration	10 years	1, 5 years; life time
Time horizon	Lifetime	1, 10, 20 years
Source: asthma related mortality	Watson 2007 + NRAD	Roberts 2013 Watson 2007 Watson 2007 + De Vries 2011 +15% Watson 2007 + De Vries 2011
Source: health state utility values	SGRQ mapped to EQ-5D	EQ-5D
Source: duration utility decrement	Lloyd 2007	MENSA
% Discontinuation beyond year 1	10%	0, 20%
Source clinical efficacy omalizumab	NMA/INNOVATE	EXALT
Average annual cost of omalizumab	£11,370	£8,056
Discount rate effects	3.5%	1.5%
Inclusion long term OCS impact (see later)	No	Yes

i) Mepolizumab (+PAS) versus SoC alone (MENSA)

Table 147 Results of the scenario analysis: Mepolizumab versus SoC alone (direct evidence)

1	ITT					GSK proposed population excluding mOCS users with <4 exacerbations					GSK proposed population				
	Total cost	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**	**Total cost**	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**	**Total cost**	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**
Base case															
Mepo + SoC	[redacted]														
SoC					£31,659					£15,394					£19,526
Age at baseline: 30 years															
Mepo + SoC	[redacted]														
SoC					£52,443					£25,289					£35,055
Age at baseline: 65 years															
Mepo + SoC	[redacted]														
SoC					£36,903					£17,384					£22,705
Biologic treatment duration: 5 years															
Mepo + SoC	[redacted]														
SoC					£31,966					£15,507					£19,803
Biologic treatment duration: Life time															
Mepo + SoC	[redacted]														
SoC					£32,130					£15,571					£19,763
Time horizon: 1 year															
Mepo + SoC	[redacted]														
SoC					£74,626					£35,626					£56,961
Time horizon: 10 years															
Mepo + SoC	[redacted]														
SoC					£47,517					£22,087					£30,252
Time horizon: 20 years															
Mepo + SoC	[redacted]														
SoC					£37,003					£17,294					£22,630
Source of asthma related mortality: Roberts 2013															
Mepo	[redacted]														

+ SoC															
SoC					£57,652					£27,795					£39,396
Source of asthma related mortality: Watson 2007															
Mepo + SoC															
SoC					£47,020					£21,850					£29,833
Source of asthma related mortality: Watson 2007 + De Vries 2011 + 15% [approximated NICE TA278 approach]															
Mepo + SoC															
SoC					£21,035					£13,318					£15,645
Source of asthma related mortality: Watson 2007 + De Vries 2011 [approximated NICE TA278 approach without + 15%]															
Mepo + SoC															
SoC					£22,379					£13,854					£16,442
Source of health state utilities: EQ-5D (DREAM)															
Mepo + SoC															
SoC					£40,392					£18,429					£20,863
Source of duration of utility decrement for an exacerbation: MENSA															
Mepo + SoC															
SoC					£32,480					£15,690					£19,963
Discontinuation beyond year 1: 0%															
Mepo + SoC															
SoC					£31,418					£15,305					£19,326
Discontinuation beyond year 1: 20%															
Mepo + SoC															
SoC					£31,994					£15,516					£19,792
Discount rate: 1.5%															
Mepo + SoC															
SoC					£27,823					£13,865					£17,200

The results of the scenario analyses for mepolizumab compared with SoC alone in the ITT and GSK proposed populations are provided in Table 147. In the GSK proposed population the ICER shows sensitivity to the age of the patient at baseline. The ICER exceeded £35,000 / QALY gained for patients aged 30 at baseline and is due to a reduced mortality risk associated with a lower age group. The ICER also shows sensitivity to the time horizon of the model, which exceeds £50,000 /QALY gained based on a one year time horizon. This is the result of a short time horizon not allowing the cumulative benefit of mepolizumab to be truly captured. Assuming a time horizon of 10 years to mirror the assumed biologic therapy duration for those who continue on therapy the ICER reached £30,252 / QALY gained.

The ICER varied considerably depending on the underlying assumptions on mortality. In the basecase we assume patients are at risk of asthma related mortality irrespective of the type of exacerbation experienced. In the GSK proposed population the ICER reduced to £15,645 / QALY gained based on our approximated replication of the NICE Assessment Group's approach in the omalizumab MTA (TA 278). Conversely the ICER increased to £29,833 / QALY gained when asthma related mortality was only applied to hospitalised exacerbations based on Watson 2011. When Roberts 2013 asthma related mortality is applied to hospitalised exacerbations, the ICER increases to £39,396 / QALY gained. However the relevance of Roberts 2013 is unclear; case fatality by patients with severe asthma is not specifically defined and the long timeframe (28 years) over which the analysis was completed questions the applicability since care is likely to have changed. The true asthma related mortality is likely to lie somewhere in between NICE's approach and Watson 2011, recognising that the numbers taken from NRAD in the basecase are meant as proxys for risk of asthma related mortality outside of a hospital setting.

ii) Mepolizumab (+PAS) versus omalizumab and SoC alone (NMA derived)

A range of scenario analyses were also considered for the comparison of mepolizumab versus omalizumab and SoC alone (efficacy derived from the NMA). In all scenarios mepolizumab remained dominant versus omalizumab however the Committee are asked to refer to the confidential addendum for a comparison of mepolizumab and omalizumab with the assumed PAS priced modeled for omalizumab.

Table 148 Results of the scenario analysis: Mepolizumab versus SoC alone and versus omalizumab (indirect evidence)

	ITT				
	Total cost	**∆ Costs**	**Total QALYs**	**∆ QALYs**	**ICER (vs.)**
Base case					
Mepo + SoC	[redacted]		[redacted]		
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£31,618**
Age at baseline: 30 years					
Mepo + SoC	[redacted]		[redacted]		
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£52,408**
Age at baseline: 65 years					
Mepo + SoC	[redacted]		[redacted]		

Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£36,858**
Biologic treatment duration: 5 years					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£31,905**
Biologic treatment duration: Life time					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£32,096**
Time horizon: 1 year					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£74,454**
Time horizon: 10 years					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£47,466**
Time horizon: 20 years					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£36,958**
Source of asthma related mortality: Roberts 2013					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£57,626**
Source of asthma related mortality: Watson 2007					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£46,980**
Source of asthma related mortality: Watson 2007 + De Vries + 15% [approximated NICE TA278 approach]					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£21,002**
Source of asthma related mortality: Watson 2007 + De Vries [approximated NICE TA278 approach, without + 15%]					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£22,344**
Source of health state utilities: EQ-5D (DREAM)					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£40,322**
Source of duration of utility decrement for an exacerbation: MENSA					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£32,439**
Discontinuation beyond year 1: 0%					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£31,390**
Discontinuation beyond year 1: 20%					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£31,938**
Equal efficacy before continuation: Omalizumab has the rate exacerbations as mepolizumab					

Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£31,618**
Equal efficacy before continuation: Mepolizumab has the rate exacerbations as omalizumab					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£33,079**
Source of clinical efficacy for omalizumab, post 16 weeks: EXHALT					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£31,618**
Average annual cost of omalizumab: £8,056					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£31,618**
Discount rate: 1.5%					
Mepo + SoC	[redacted]	[redacted]	[redacted]	[redacted]	
Oma + SoC	[redacted]	[redacted]	[redacted]	[redacted]	**Dominant**
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£27,787**

5.8.4 Scenario analysis: Inclusion of long term cost and consequences of maintenance OCS

Long-term exposure to OCS use is associated with significant short and long term morbidity including but not limited to fracture/osteoporosis, cataract, diabetes, myocardial infarction, peptic ulcer and stroke, all of which are associated with increased morbidity.[24,25,207-211]

In the base case analyses the population includes people on mOCS but does not evaluate the long term costs and consequences associated with taking mOCS and therefore the possible health benefits and cost savings associated with reducing the exposure to mOCS whilst on mepolizumab. In a scenario analysis the cost and consequences associated with reducing exposure to maintenance OCS for mepolizumab patients has been explored.

Previous approaches to modeling the costs and consequences of OCS in severe asthma

The NICE Assessment Group (TA 278) undertook a similar analysis in the recent omalizumab MTA. Briefly, a cohort of OCS users was considered and the following assumptions made:

- OCS bursts due to clinically significant exacerbations do not increase the risk of OCS-related adverse effects and have negligible costs.
- The excess risk of OCS is based solely on current exposure to OCS and once patients discontinue OCS, excess relative risk becomes negligible.
- Patients who discontinue OCS restart OCS if omalizumab treatment is discontinued.
- Patients who do not receive omalizumab receive maintenance OCS for the remainder of their life.

Excess relative risk was considered for Type II diabetes, myocardial infarction, osteoporotic fracture, glaucoma, ulcer, cataracts and stroke. Risks were taken from a number of papers identified through a systematic search. Aggregated HRQL burden was obtained from the World Health Organization global burden of disease report.[166] The study reports DALY burden across a number of conditions and this was applied with the assumption that DALYs are equivalent to QALYs. Aggregate costs were taken from the average annual cost of each outcome weighted by its excess relative risk plus the cost of OCS. OCS cost was based on the dose recorded at baseline in EXALT and APEX (13.1mg and 18.56mg of prednisolone respectively). The analysis was conducted in a population, which were all on maintenance OCS. The result of this scenario analysis reduced the reported base case ICER in this sub-group by £4,000-£6,000/QALY gained[152,159] and £10,000-£17,000/QALY gained.[170]

Scenario analysis of OCS sparing: Inputs
GSK undertook a longitudinal cohort design study, utilising the Clinical Practice Research Datalink (CPRD) to examine the dose dependent risk of developing 6 AEs (diabetes, peptic ulcer, osteoporosis, cataracts, stroke and myocardial infarction) associated with systemic corticosteroid therapy in a severe asthma population (study report available on request from GSK and model equation is summarised in appendix 8.16). CPRD electronic medical records were linked to Hospital Episode Statistics (HES) data containing details of hospital admissions, hospital based outpatient appointments and A&E encounters. Data extracted were restricted to a population of severe asthma patients defined by GINA Step 4/5 guidelines (which reflect the BTS/SIGN guidelines). The observation period was limited to January 1st 2004 to March 31st 2012. The risk of developing an OCS related AE was contrasted between a mepolizumab eligible population (a severe asthma population) and a non-mepolizumab population as a function of OCS dose. The average cumulative OCS dose represented the key independent variable and the impact of an increase in OCS was measured in a liner model. The study ascertained hazard ratios and probability of events under conditions of time dependent OCS use (a Cox proportional hazard model was used with time varying covariates, to derive the hazard ratios). Specifically, the hazard ratio of an event due to a patient receiving an additional gram in the average cumulative maintenance OCS dose was estimated.

Table 149 shows the relative risks across a number of long term consequences as identified by the CPRD study. The table shows that the relative risks are not directly comparable to those used in the recent omalizumab appraisal.[170] Indeed, the magnitude of the risk is lower for most events. Differences are likely due to our incident user design which meant that a large proportion of eligible patients were taking low doses of mOCS and this helps to explains why the reported hazard ratios are likely to be low. At baseline in the CPRD study, 74.3% of the overall cohort were not taking maintenance OCS, 21.7% were taking between 0 and 2.5mg of OCS daily. The remaining 4% of the cohort were taking higher doses.

This suggests that the CPRD study population is not reflective of the mepolizumab clinical trial population who are on higher mOCS doses (13.2mg in MENSA). The CPRD population is therefore on average likely to experience fewer OCS-related AEs than the mepolizumab population. To some extent this is overcome in the modelling since the RRs applied reflect the risk per gram of OCS dose received and therefore is ‘scaled up’ proportionately for the mepolizumab patients who receive

more OCS on average (i.e. the RR gets multiplied by number of grams of dose received). However this becomes an issue when the RR of an event is not linear in terms of the magnitude of the dose of OCS; there are categorical RRs which do not follow a linear form. These RR's are not comparable to the one's used in the model because they are the average RR for that dosing category- rather than the additional risk per gram of dose. Therefore, results derived from a population who are less severe and receiving a lower mOCS dose (the CPRD population) are unlikely to be truly informative for the severe refractory eosinophilic asthma population modelled.

Other reasons may include limited prior information on historical exposure to OCS, as well as general coding limitations in longitudinal databases. Table 150 shows the differences in baseline incidences for events reported in Manson et al (2009) and those identified through the CPRD database analysis. It is difficult to directly compare these values as the GSK CPRD study presents cumulative exposure whereas the literature reported RRs based on a variable dose exposure.

Table 149 Relative risks of an event due to exposure to maintenance OCS.

	Used in previous NICE Technology Assessment Report (NICE TA278)[170]				**GSK CPRD study**
Definition of relative risk applied	Relative risk of event due to maintenance OCS use vs. no use				Relative risk of event due to additional g of average cumulative maintenance OCS dose vs. no use per 28 day period
		Original source	**OCS Dose reported in publication**		
Diabetes	3.02	Gurwitz et al (1994)[212]	10-19.75mg		1.38
MI Subjects followed up from start date to earliest occurrence of end points	2.50	Varas-Lorenzo et al (2007)[213] From start date to earliest occurrence of end points	>10mg		1.36
Osteoporosis Patients followed up anywhere from 1987-1997; 10 predictive risk model	2.84	Van Staa et al (2005)[214]	15-29.9mg		2.09
Glaucoma	1.37	Garbe et al (1997)[215]	10-20mg		Not reported
Peptic ulcer	2.00	Piper et al (1991)[216]	All doses		1.22
Cataract	1.83	Curtis et al (2006)[217]	>6.5mg		1.95
**Stroke was also considered as part of the CPRD study however was found to have a protective or neutral effect, contradicting the previous NICE appraisal of omalizumab, Manson (2009) and clinical expectations. The reason for this finding is not well understood (speculative). Stroke was also not implemented in the NICE omalizumab appraisal*					

Table 150 Baseline incidence comparison for patients (Manson (2009) vs. GSK CPRD study)

	Baseline probability	
	UK population level estimates presented in Manson et al (2009) – incidence per year	**GSK CPRD study estimates± - incidence per year**
Diabetes	0.0038	0.0089
MI	0.0039	0.0013
Osteoporosis	Not reported	0.0054
Peptic ulcer	0.0012	0.0028
Cataract	0.0043	0.0043

±. The probabilities presented in the table are the probabilities based on first year (13 28-day periods) cumulative baseline hazard (i.e. year 1 baseline incidence) for no systemic corticosteroid use and the other covariates in the models are set to their mean values in the study.

A targeted literature search was undertaken to identify resource use/cost and utility values associated with OCS-related AEs specifically, cataract, diabetes, fracture, myocardial infarction and peptic ulcer. Details of the targeted search terms can be found in Appendix 8.16, searches were conducted on 16th July 2015. From 2,691 indentified records, 156 articles were screened for full-text selection but only two articles were selected for inclusion. Utility values and resource use/costs of OCS related AEs were identified in Sullivan et al (2011)[218] and Manson et al (2009)[24] respectively. Both of these papers are discussed in more detail below. The full systematic review report is provided in the reference pack.[164]

Disutilities assumed for the long-term consequences of OCS

In a similar scenario analysis completed for the NICE omalizumab MTA (TA278), health losses were taken from a World Health Organisation study on global burden of disease[166]. The study reports DALY burden across a number of causes and this were applied with the assumption that DALYs are equivalent to QALYs. For this scenario analysis, the disutility (as opposed to DALYs in the omalizumab appraisal) associated with diabetes, MI osteoporosis peptic ulcer and cataract were taken from Sullivan et al (2011), a catalogue of EQ-5D scores for the UK.[218] The study utilised data from a 2000, 2001, 2002 and 2003 Medical Expenditure Panel Survey (MEPS) which contained 79,522 individuals with valid EQ-5D index scores based on a UK community scoring function (see Table 151). Censored least absolute regressions were used and resulting co-efficients were reported without manipulation. The reported co-efficients were re-calculated to provide a decrement applied per cycle of the model (for osteoporosis and diabetes) or as a one off decrement (cataract, acute myocardial infarction and gastroduodenal ulcer) to the proportion of patients at risk of the OCS related event in question.

Table 151 Summary of disutility applied for the long term consequences of OCS (taken from Sullivan et al., 2011)[218]

	N	Co-efficient*	SE
Cataract	1664	-0.0271	0.006
Acute myocardial infarction	496	-0.0557	0.011
Gastroduodenal ulcer	470	-0.0552	0.014
Osteoporosis	1412	-0.0418	0.006
Diabetes without complications	5914	-0.0621	0.004

**applied a disutility in the economic evaluation*

Costs associated with the long term consequences of OCS

Costs associated with the long term consequences of OCS were taken from Manson et al (2009), which took a UK perspective and utilised UK cost data where possible. A search was undertaken between January 1990 and March 2007. Sixty one studies were identified including 21 different categories of OCS related adverse events, with fracture risk most frequently reported. An economic analysis was performed to estimate the additional economic burden caused by OCS-related adverse events. For fracture, cataract, diabetes, peptic ulcer, stroke, myocardial infarction and non-Hodgkin's Lymphoma that reported a RR, the baseline incidence of AEs was subtracted to identify the number of AEs due to OCS. This was then multiplied by the overall population incidence rate to determine the additional number of AEs caused uniquely by OCS in patients receiving treatment. The cost per AE episode or cost per year of AE treatment was applied to calculate the overall cost per OCS treated individual.

Table 152 Costs applied to the long term consequences of OCS related AEs

OCS-related Adverse event	2007 Cost per episode / year[24]	Indexed to 2014 cost	SE +/-20%
Cataract	£890.67	£1006.77	£201.35
Acute myocardial infarction	£1,369.95	£1,548.52	£309.70
Gastroduodenal ulcer	£10,163.28	£11,488.07	£2,297.61
Fracture*	£6,541.12 or £131.12 per patient taking OCS	£15.21	£3.04
Diabetes without complications	£2,519.86	£2,848.32	£569.66

**Likely an underestimate, incorporates cost of treating a fracture rather than osteoporosis.*

Approach to estimating the impact of OCS reduction

The scenario analysis is conducted for the entire patient cohort i.e. not just those patients on mOCS at baseline. This is to reflect the likely population for whom mepolizumab will be used in. We assumed that 25% of patients are on maintenance OCS at baseline in line with the base line characteristics of patients recruited to MENSA. Two approaches are explored: a dose reduction approach and discontinuation approach.

i) Dose reduction approach

This approach assumes that treatment with mepolizumab reduces the average OCS dose. Like the omalizumab appraisal it is assumed that infrequent OCS bursts due to clinically significant exacerbations do not increase the risk of OCS-related adverse events. The dose reduction approach applies the median dose reduction for mepolizumab versus SoC alone observed in SIRUS at 24 weeks (a 30% dose reduction; median implemented since the dataset is highly skewed). The incremental difference in dose reduction is applied in both arms. The daily OCS

dose of patients after 24 weeks on mepolizumab is 9.24 mg. It is assumed that patients who discontinue on mepolizumab return to the OCS dose applied to the SoC arm, 13.2mg.

ii) Discontinuation approach
The OCS sparing analysis in the omalizumab appraisal followed a discontinuation approach where a proportion of patients are assumed to stop OCS maintenance treatment at a certain time point.[170] The relative risks of OCS related adverse events applied in this approach reflect the risk associated with receiving OCS maintenance therapy relative to not receiving any maintenance OCS, and are reflective of the average dose received by cohort. By removing any probability of OCS related adverse events for a proportion of the cohort, rather than simply decreasing the probability, this approach shows a larger difference in the rates of adverse events (and therefore the economic impact) between treatment and standard of care than in the dose reduction approach. Data from SIRIUS showed that in the mepolizumab arm 6.9% of patients completely discontinued OCS versus SoC alone. Therefore 22.3% of patients continue on OCS where daily OCS remains at 13.2mg. It is assumed that a patient who discontinues on mepolizumab restarts on the OCS dose applied to SoC alone (13.2mg).

The two approaches are summarised in Table 153. The results of two approaches are shown in Table 154 and Table 155.

Table 153 Key assumptions in the two OCS sparing scenario analyses

Dose reduction approach	Discontinuation approach
Treatment with mepolizumab reduces the average OCS maintenance dose (treatment effect based on median dose reduction seen in SIRIUS) at 24 weeks. The median difference in the median % reduction in daily OCS dose was 30% less for mepolizumab versus SoC.	Treatment with mepolizumab causes a proportion of patients to discontinue maintenance OCS at 24 weeks (SIRIUS, 6.9%, the differential proportion of patients). Note the modelling approach uses the n of patients discontinuing / N.
Infrequent OCS bursts due to clinically significant exacerbations do not increase the risk of OCS-related adverse effects and have negligible costs.	Same as the dose reduction approach
Excess risk attributable to OCS is based on average cumulative dose and the previous dose. Once patients discontinue OCS, the excess relative risk becomes negligible.	Same as the dose reduction approach
Patients who experience dose reduction receive the higher dose of OCS if mepolizumab treatment is discontinued	Patients who discontinue OCS restart OCS if mepolizumab treatment is discontinued

Discussion to the OCS sparing scenario analysis

The inputs used in the OCS sparing scenario analysis demonstrated a lower baseline risk of adverse events, plus a smaller utility detriment associated with OCS use then had previously been observed in the literature. The OCS sparing analysis assumes a treatment benefit only at 24 weeks, and is carried out for the entire population, rather than just for the population of patients on mOCS. For these two reasons, the impact of the scenario analysis is smaller than what clinical opinion

might expect and less than what has been demonstrated in previous analyses. There was a limited reduction in the resultant ICER, compared to the similar scenario analysis undertaken by the NICE Assessment Group for omalizumab which for a cohort of patients, all on maintenance OCS, showed an improvement by £4,000-£6,000/QALY gained[152,159] and £10,000 - £17,000 /QALY gained.[170] In the GSK proposed population implementing the dose reduction approach and assuming 24% of patients are on mOCS reduced the ICER by only £26, to £19,500 / QALY gained. By implementing the discontinuation approach the ICER decreased by £4 to £19,522

In the dose reduction approach, the treatment benefit for mepolizumab over SoC is given as the difference in the median percentage daily dose reduction in maintenance OCS at 24 weeks as observed in SIRIUS. The magnitude of the daily OCS dose impacts the probability of OCS related adverse events which are in turn associated with costs and disutilities. In this approach, the same proportion of each arm is assumed to be on mOCS (assumed to be 24% to reflect the MENSA population) and at baseline any patient on mOCS is assumed to be receiving 13.2mg per day (MENSA). At 24 weeks a 30% treatment effect in the median percentage daily dose reduction was observed for mepolizumab in SIRIUS. Therefore, in the economic model mepolizumab mOCS patients receive 9.24mg mOCS per day after week 24 (i.e. 30% reduction). Since only one dose reduction is conservatively assumed across the time horizon, the overall reductions in the average cumulative dose for the mepolizumab arm are moderate in magnitude in terms of mg, and are of a small magnitude in terms of grams. The relative risks of experiencing the OCS adverse events are those derived from the CPRD study, they demonstrate the increased probability of an event over a 28 day period, as a result of receiving an additional gram of OCS dose. Therefore, only a small incremental difference in the cycle specific probabilities of adverse events between mepolizumab and SoC is observed as a result of the reduction in daily mOCS dose. Hence the resultant ICER is not shifted significantly. This issue is further compounded by the fact that the relative risks derived and the baseline probabilities of events observed in CPRD are smaller than those previously used in economic evaluations of OCS sparing (discussed earlier). Additionally, only a percentage of the entire cohort is assumed to be on mOCS at baseline.

However, applying a discontinuation approach did not seem to improve the ICER any more than the dose reduction approach to OCS sparing. Although, this approach has also been implemented in the mepolizumab economic model it does not demonstrate the same magnitude of effect as in previous analyses. This is likely due to the size of the relative treatment effects used; we observed a 6.9% discontinuation rate at 24 weeks where as omalizumab assumed a 40% discontinuation rate at 32 weeks. Additionally in the mepolizumab analysis only a proportion of the cohort are assumed to be mOCS users. However, in previous economic evaluations of OCS sparing for omalizumab, this analysis was carried out for an entire population of mOCS users.

Table 154 Scenario analysis: OCS sparing; implementing a dose reduction approach

	ITT					GSK proposed population excluding mOCS users with <4 exacerbations					GSK proposed population				
	Total costs	Δ Costs	Total QALYs	Δ QALYs	ICER	Total costs	Δ Costs	Total QALYs	Δ QALYs	ICER	Total costs	Δ Costs	Total QALYs	Δ QALYs	ICER
Base case: long term costs and consequences of OCS not captured															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£31,659	[redacted]	[redacted]	[redacted]	[redacted]	£15,394	[redacted]	[redacted]	[redacted]	[redacted]	£19,526
Assumes 24% of patients are on maintenance OCS (MENSA)															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£31,608	[redacted]	[redacted]	[redacted]	[redacted]	£15,375	[redacted]	[redacted]	[redacted]	[redacted]	£19,500

Table 155 Scenario analysis: OCS sparing; implementing a discontinuation approach

	ITT					GSK proposed population excluding mOCS users with <4 exacerbations					GSK proposed population				
	Total costs	Δ Costs	Total QALYs	Δ QALYs	ICER	Total costs	Δ Costs	Total QALYs	Δ QALYs	ICER	Total costs	Δ Costs	Total QALYs	Δ QALYs	ICER
Base case: long term costs and consequences of OCS not captured															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£31,659	[redacted]	[redacted]	[redacted]	[redacted]	£15,394	[redacted]	[redacted]	[redacted]	[redacted]	£19,526
Assumes 24% of patients are on maintenance OCS (MENSA)															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£31,649	[redacted]	[redacted]	[redacted]	[redacted]	£15,391	[redacted]	[redacted]	[redacted]	[redacted]	£19,522

5.9 Validation

5.9.1 Validation of de novo cost-effectiveness analysis

Two advisory boards with respiratory clinicians and UK health economists were also undertaken (see Section 2 and Section 5.3) to test the clinical assumptions underpinning the model and approach to the modelling in general. Discussions which materially affected our approach included the model structure (exacerbations as a health state versus a transient event) as well as advice for deviating from the NICE Reference Case with regards to utilising SGRQ (from MENSA) derived utilities over EQ-5D collected in Phase IIb study DREAM. During the iterative process of the economic evaluation development, the model underwent interim QCs by the model developers (Pharmerit). Further the model also underwent two rounds of QC performed by an additional third party vendor (ICON). A QA was performed by a GSK analytics group and covered a critique of the following:

– Completeness of model documentation and availability of the model (Excel/VBA application)
– General checklist of validity and credibility of the model
– Completeness and accuracy of reporting of model results

5.10 Interpretation and conclusions of economic evidence

Note that the discussion here relates to the model structure, inputs and QALY gains associated with the add-on mepolizumab (PAS price) and comparators, SoC alone and add-on omalizumab (List price). The ERG and Committee are advised to review the confidential addendum to this submission which provides the cost-effectiveness analyses at the PAS prices for mepolizumab and omalizumab (estimated).

We believe we have made a reasonable attempt at demonstrating the cost-effectiveness of mepolizumab versus SoC alone and versus omalizumab (for the overlap population) using a relatively simple and conservative modelling approach. We have attempted to remain transparent and explicit about the assumptions within the model.

During the development of the mepolizumab economic model careful consideration was given to the Assessment Group's evaluation and critique and the dialogue that ensured with the NICE Committee with regards to the recent MTA of omalizumab (TA 278).[137,170] We have purposefully sought to rectify and act upon those criticisms and data applications in the mepolizumab submission.

Comparison to the approach taken in the omalizumab appraisal

The systematic review of the economic literature did not identify any relevant published studies assessing the cost-effectiveness of add-on mepolizumab relevant to this appraisal, so it is not possible to make comparisons with published literature for the intervention of interest. However the recent NICE MTA appraisal of omalizumab (TA278), and published economic literature of the clinical effectiveness

of omalizumab, does allow methods and findings to be compared to test, to some extent, the face validity of this economic evaluation.

The two model structures are similar, considering the day-to-day asthma symptoms whilst on therapy, to the point of assessment continuation criteria. Both models apply a continuation criteria but differ in their approaches based on the SmPC of the respective interventions; mepolizumab applying exacerbation-based continuation criteria at 52 weeks with a small proportion of patients reverting back to standard of care (<10%); omalizumab applying a single item physician rated continuation criteria at 16 weeks and with much larger proportion of patients reverting back to SoC at that point (43.5% from an RCT setting[58] and 29.9% in an open label setting[74]).

One key difference is that whilst in the omalizumab model structure exacerbation events were considered as separate states (clinically significant exacerbation [PEF or FEV_1>60% of personal best] and clinically significant severe exacerbation [PEF or FEV_1<60% of personal best]), in this model the risk of an exacerbation event is considered a 'transient event' whilst in the day-to-day asthma symptom state. This somewhat simplifies the modelling engine without impacting on the overall model results. In both models, a life time horizon was modelled, 10 years biologic treatment duration was assumed and no AEs were modelled (from either the biologic or from OCS [basecase])

Day-to-day utility is drawn from SGRQ scores mapped to EQ-5D. Whilst EQ-5D was captured at 4-weekly intervals in the phase IIb 52 week dose ranging study DREAM the results showed that approximately one third of patients at baseline reported perfect health. This is unusual considering the severity of the patient population and the HRQL of these people described by respiratory clinicians. As a result of this finding EQ-5D was not included in the Phase III mepolizumab trial programme as those patients in 'perfect health' would be unable to demonstrate any improvement as a result of therapy. Therefore SGRQ values captured in the Phase III MENSA trial were mapped to EQ-5D for the base case but for completeness directly elicited EQ-5D values were included in a scenario analysis. In the omalizumab MTA the Assessment group chose, despite the limitations and possible bias of open label data, to use directly elicited EQ-5D values captured in EXALT[74]. The systematic literature review of HRQL of asthma patients showed that overall utility values for patients reporting symptoms was lower regardless of treatment and varied from 0.669-0.85 (see Section 5.4.3). This gives some validity to the resultant EQ-5D scores mapped from SGRQ with patients on add on mepolizumab observing a utility of 0.796 (SE 0.010) in the ITT population, 0.793 (SE 0.021) in the GSK proposed population excluding mOCS users with <4 exacerbations and 0.777 (SE 0.017) in the GSK proposed population at baseline.

When comparing the difference in EQ-5D values between those reported in the omalizumab assessment (vs. SoC) and those utilised in this economic evaluation for mepolizumab the resultant utility values are broadly similar for the ITT population. The difference in EQ-5D values between omalizumab responders and patients on SoC in the overall EXALT population was 0.048 versus a difference of 0.068 in EQ-5D mapped from SGRQ for responders to mepolizumab versus SoC alone. Whilst a direct comparison cannot be made the same trends are also observed; that by

restricting to a more severe patient population this has the effect of increasing the observed difference between the biologic and SoC alone arms.

To provide a more accurate costing and associated disutility of an exacerbation event, 3 types of exacerbations were included; those requiring OCS, an ED visit or a hospitalisation. The disutility of an exacerbation and duration applied was taken from a UK study (Lloyd 2007), also implemented by the Assessment Group in the omalizumab appraisal. We have taken a conservative approach and assumed the same disutility for an exacerbation requiring OCS and one requiring an ED visit in the absence of evidence to support otherwise (-0.10).

Asthma-related mortality was identified as a key driver of cost-effectiveness in the recent omalizumab NICE MTA. Feedback from respiratory clinicians reported that this severe asthma population were at risk of asthma-related mortality. In the NICE omalizumab MTA, the risk of asthma related mortality was applied to all modelled patients, as a probability per 3 month cycle of 0.001 based on a study by De Vries 2011. Later the Assessment Group were asked to assume a mid-point between de Vries and Watson plus 15%.[137] Faria (2014) shows that the ICER decreases, with an increase in mortality risk.[159] The NICE MTA and clinician feedback provided support of asthma-related mortality both in a hospital setting and in the community. We set about identifying any updates to the published literature and only two were initially deemed useful; Watson[167] and Roberts[173]. Watson was deemed preferable to Roberts, since Roberts required absolute deaths to be estimated that may differ from the observed data, the definition of severe asthma was not specifically defined and the long study period over which care is likely to have changed. Watson provided a risk of asthma related mortality for severe asthma patients who exacerbate and require hospitalisation. To estimate the risk of asthma-related mortality for exacerbations requiring an OCS and ED visit we re-visited the NRAD report[49] of asthma deaths. Whilst realising the source of this data was not confined to a severe asthma population we believe the deaths provided by location at least provided a proxy to estimate a risk of mortality outside of a hospital setting. We then considered a number of scenario analyses varying asthma-related mortality assumptions which also included an attempt to replicate the NICE Assessment Group's approach (Section 5.3.6). All-cause mortality is applied to the whole population which does also include some asthma deaths although unlikely to impact the cost-effectiveness results.

Overall despite some differences in approach, the comparison to the NICE appraisal of omalizumab (TA278) does provide some face validity for the economic model structure assumed here.

Interpretation of the results of the economic evaluation

Mepolizumab versus SoC alone in the GSK proposed populations
The base case cost-effectiveness results show that in the GSK proposed population the ICER (PSA derived) of mepolizumab versus SoC alone is £19,511 / QALY gained compared with £15,478 / QALY gained in the GSK proposed population excluding mOCS users with <4 exacerbations (Section 5.8.1). The higher ICER in the GSK proposed population reflects the smaller differential in day-to-day utility between patients on mepolizumab and SoC alone when a population includes both

exacerbating or on mOCS patients (0.042 utility points smaller). It is likely that for those patients on mOCS their daily asthma symptoms are more controlled compared with an exacerbating patient not on mOCS. However in both populations mepolizumab provides a cost effective use of NHS resources.

The deterministic univariate sensitivity analyses (Section 5.8.2) showed that in the GSK proposed populations the ICER was sensitive to the same set of parameters, namely SoC SGRQ derived utility, exacerbation rate and utility assumed for continued mepolizumab patients, overall exacerbation rates assumed for SoC alone and asthma related mortality (applied to exacerbations requiring hospitalisation). In all instances the ICER remained below £25,000/QALY gained).

An extensive number of scenario analyses were conducted (Section 5.8.3). In the GSK proposed population the ICER is sensitive to the baseline age of the patient cohort, rising to £35,055 / QALY gained for a cohort at 30 years which is driven by the reduction in the assumed mortality risk and the potential for a greater proportion of the population to remain on treatment for 10 years. However feedback from respiratory clinicians from the advisory boards suggests that the mepolizumab clinical trials are reflective of a late onset population, likely in their 4th and 5th decade consistent with the demographics of patients recruited to the clinical trials. A scenario analysis was also conducted to explore the ICER implementing directly elicited EQ-5D values from the phase IIb study DREAM. In the GSK proposed population this worsened the ICER to £20,863 as a result of reducing the incremental QALYs by [redacted]. However we strongly believe this generic instrument is not sensitive enough for use in this severe asthma population and fails to capture key HRQL domains in these patients (see Section 5.4.1).

As discussed in Section 5.3.6 given the learnings from the NICE omalizumab MTA we were aware that asthma related mortality was likely to be driver of the cost-effectiveness for mepolizumab. The basecase applies an asthma related mortality risk to patients experiencing an exacerbation requiring an OCS burst (NRAD proxy), and ED visit (NRAD proxy) and a hospitalisation (Watson 2007). The scenario analyses showed that we if take a like-NICE approximation (mid-point of Watson and De Vries + 15%) the ICER further improves to £15,645 / QALY gained in the GSK proposed population including OCS. Conversely if we assume asthma-related mortality only happens as a result of an exacerbation requiring a hospitalisation the ICER worsens to £29,833 / QALY gained (Watson 2007 applied only). Whilst the ICER rises to £39,396 / QALY gained when Roberts 2013 is applied as a source of mortality, as discussed above we believe the Watson and NRAD mortality assumptions to be more relevant to this appraisal.

We have also assumed a 10% year on year discontinuation rate for patients on biologic therapy post-continuation review in year 1 (based on the withdrawal rate observed in COSMOS). We do not believe it realistic to assume that 100% of patients meeting continuation criteria would remain on biologic treatment in clinical practice. The scenario analysis shows that the ICER worsens if we assume that 20% of patients discontinue therapy and this is the result of an overall smaller incremental QALY gain and reduced treatment cost. In the scenario analyses conducted in the omalizumab appraisal, a 10% and 20% withdrawal rate was associated with a 20% and 40% increase in the resultant ICER respectively.[170]

OCS sparing and its impact on the ICER

The OCS sparing scenario analysis based on a CPRD observational study undertaken by GSK, demonstrated a lower baseline risk of adverse events, plus a lower utility detriment associated with OCS use then had previously been observed in the literature. An OCS dose reduction and discontinuation approach were explored but the scenario analyses did not generate the expected upside of sparing patients from OCS. The results are in contrast to those from the approach taken in the NICE omalizumab MTA which showed an improvement by £4,000-£6,000/QALY gained[152,159] and £10,000 - £17,000 /QALY gained.[170]

Feedback from clinical advisers suggests these approaches do not capture the true benefit of reducing mOCS and given the significant health impact of oral steroids this analysis lacks the face validity when the impact on resulting cost/QALYs are marginal. However there are a number of known limitations in the analysis presented. The CPRD population appeared to be less severe that the severe refractory eosinophilic asthma population of interest here. Additionally a linear model was assumed so for an RR of an event that is not linear (by dose of OCS) these RR's are not comparable to the one's used in the model because they are the average RR for that dosing category- rather than the additional risk per gram of dose. Only a limited number of OCS related AEs are captured and further no short term OCS related AEs are considered such as Addison's disease, oedema, weight gain, sleep disturbance, anxiety of taking OCS etc. The BTS/SIGN guidelines also advise that patients on long-term steroid tablets (for example, longer than three months) or requiring frequent courses of steroid tablets (for example, three to four per year) who are therefore at risk of systemic side effects should be monitored regularly for e.g. blood pressure, urine or blood sugar and cholesterol (diabetes mellitus and hyperlipidaemia), and bone mineral density in adults for risk of osteoporosis and the costs of these additional tests have not been included.[22] We would therefore argue that whilst the estimates of a £4,000 - £17,000 reduction from the omalizumab appraisal have not been supported by this new analysis these current estimates are highly conservative and that the ICER would reduce further if more aggressive estimates were included.

Mepolizumab (+ PAS) comparison with list price add-on omalizumab.

The comparison versus add-on omalizumab is limited by the availability of the relevant omalizumab data for the NMA as outlined in Section 4.10. An indirect comparison could not be made in the truly relevant population – the GSK proposed population and the omalizumab eligible population for which NICE has issued positive restricted guidance due to the lack of IPD for omalizumab. However, a comparison of the full trial populations based on three end points for which data were available favoured mepolizumab. We believe we are at least in a position to state that mepolizumab is at least as effective as omalizumab in the full trial population. The restricted populations for omalizumab and mepolizumab are similar and in both cases there is evidence that supports improved effectiveness in these more severe populations. Therefore we believe it is a reasonable assumption that if the populations were restricted similarly this conclusion would still be clinically valid.

The results of this section must be caveated with the limitations of the NMA and also the use of the list price for omalizumab. In the full ITT where mepolizumab is compared with omalizumab (based at list price) the PSA derived ICER is dominant with cost savings of [redacted] and incremental QALY gains of [redacted]. The univariate sensitivity analysis showed that this comparison was sensitive to the proportion of patients meeting the continuation criteria for omalizumab therapy, proportion of patients who discontinue and the exacerbation rates of those patients meeting the continuation criteria for biologic therapy. In all cases the ICER remained below acceptable thresholds. In all scenario analyses mepolizumab remained dominant versus omalizumab.

We are confident that the average annual cost per patient on omalizumab is higher than the £8,056 (based on list price) reported in the NICE MTA of omalizumab.[137] Recent omalizumab guidance issued by the NCPE (Ireland) provides an additional source to our estimate and supports a real world per patient cost increase (£11,723). We believe the study conducted with IMS Health (section 5.5.2) to be robust and conducted with a high degree of integrity (for example removal of subjects with complex dosing which were difficult to categorise). The study retrospectively reviewed dose and frequency of dose from 2010 to 2014 and reassuringly, the calculated average annual cost for 2011, the time at which the NICE MTA commenced was within the region of that reported by NICE (£7,959). We have also taken a conservative approach for the base case and used the average annual cost per patient across 2010 to 2014 (£11,370) and not the average annual cost from 2014 alone (£12,027).

It should be noted that in clinical practice compared with add-on omalizumab, mepolizumab does not require any specialist testing to identify eligible patients (IgE test) beyond a routine blood test already conducted as part of a patient assessment. Conservatively, we have not included the cost of an IgE test for omalizumab which we believe to be more expensive than a standard blood test (a single RAST test alone is estimated at £15.89)[204]. Further, dosing is fixed at 100mg per 4 weeks unlike omalizumab which is based on IgE levels, weight and a two or 4 weekly schedule providing assurance of a predictable budget impact.

The ERG and Appraisal Committee should refer to the confidential addendum for a comparison including the estimated PAS for omalizumab. The results remain similar.

5.10.1 Additional areas for research

There are a number of areas of the modelling which would benefit from further research to enhance the robustness of the estimates. Ideally a study to estimate the true asthma related mortality in this severe asthma population would avoid the necessary assumptions which have been made not only in this evaluation but also in the recent MTA for omalizumab. Secondly to access the omalizumab IPD data would enable a more robust comparison of the effectiveness in the appropriate relevant patient populations to be compared.

Summary of the cost-effectiveness results

Analysis	ICER (£/QALY gained) PSA derived
Mepolizumab (+ PAS) versus SoC alone	
ITT	**£31,692**
GSK proposed population excluding mOCS users with <4 exacerbations: Blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous 12 months	**£15,478**
GSK proposed population: Blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous 12 months or are dependent on OCS	**£19,511**
Mepolizumab (+PAS) versus omalizumab (list price)	
ITT	**Dominant**

Table 156 Strengths and weaknesses of the economic evaluation

Strengths	• Uses an established modelling methodology
	• Uses a similar modelling approach as that for omalizumab, previously endorsed by NICE
	• Conservative assumptions which may serve to overestimate the cost of mepolizumab
	  o Biologic treatment continuation for 10 years
	  o Decrement in utility assumed for a ED required exacerbation assumes that of a less severe exacerbation requiring OCS
	• In the absence of head to head data comparative efficacy versus omalizumab has been attempted via a network meta-analysis
	• The model incorporates a range of scenario analyses within the DSA
	• Estimated omalizumab vial usage in NHS practice versus that reported in clinical trials to estimate the true omalizumab cost to the NHS

Limitations	Certain limitations must be acknowledged • The current economic model is based on the results of Phase III MENSA which pools bioequivalent IV and SC arms. It does not pool relevant data from Phase IIb DREAM; however we do not believe this would materially impact the results presented. Relevant DREAM data is pooled for the purpose of the NMA versus omalizumab (compares full trial populations). • The current economic model is based on the results of Phase III MENSA which may not be reflective of long term use in clinical practice (inherent in all evaluations), however COSMOS has demonstrated mepolizumab continues to be clinically effective. • We have not used directly elicited EQ-5D values from Phase IIb study DREAM, although these have been included in a scenario analysis. • Utility is derived from a mapping algorithm that has not been validated in a severe asthma population • The NMA in the 'trial' populations for mepolizumab versus omalizumab require an assumption that as both populations are restricted similarly the comparative treatment effect would also remain broadly comparable between both treatments. • The scenario analyses looking at the long term costs and consequences of OCS we believe still vastly underestimates the impact on costs and QALYs which would seek to improve the reported cost-effectiveness results for mepolizumab.

6 Assessment of factors relevant to the NHS and other parties

NOTE: This budget impact includes the list price for mepolizumab and omalizumab. The ERG and Committee are asked to refer to the confidential addendum for a budget impact based on PAS prices.

6.1 People eligible for add-on mepolizumab in England and Wales

The number of people eligible for mepolizumab based on the GSK proposed population including OCS (a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or are dependent on maintenance OCS) is estimated at 16,166 in year 1 rising to 16,558 by year 5 (see Table 157). The epidemiology data used to inform the approximation of eligible patients is taken from a sub-cut analysis of the IDEAL data.[23]

Table 157 Maximum eligible patient population

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020	Source
People ≥18 years	45,208,439	45,479,690	45,752,568	46,027,083	46,303,246	ONS; Mid-year population estimates by age and sex for local authorities in England and Wales, mid-2014.[219] 0.6% annual growth rate applied.[220]
People ≥18 years with asthma diagnosis	2705688	2721922	2738253	2754683	2771211	Quality and Outcomes Framework (QOF) for April 2013 - March 2014, England (5.93%)[221] & Wales (6.93%)[222]
People with severe asthma	5%	5%	5%	5%	5%	Chung 2014[20]
Of those patients with severe asthma, proportion eligible for mepolizumab in the GSK proposed population including OCS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IDEAL[23]
	16,166	16,263	16,361	16,459	16,558	

6.2 What assumptions were made about current treatment options market share and uptake of technologies?

Table 158 provides the estimated market share and associated patient numbers without and with the introduction of mepolizumab.

Table 158 assumes:

- Mepolizumab eligible patients are currently on SoC alone or add-on omalizumab – this does not reflect the proportion of patients who may not be captured by 'SoC' alone e.g. those patients taking immunosuppressant agents, undergoing thermoplasty etc.
- Decreasing market share for SoC alone with the introduction of mepolizumab.
- A slower increase in market share for add-on omalizumab with the introduction of mepolizumab. However an increase is expected to remain (Historic IMS data suggests that omalizumab growth is an estimated 25% year-on-year growth).
- Market share for eligible mepolizumab patients is expected to come from patients who would otherwise receive SoC alone or add-on omalizumab. However over the next 5 years with the expected introduction of further anti-IL-5 therapy this may not be reflective of clinical practice.
- Current market share of omalizumab represents omalizumab patients who would be eligible for add-on mepolizumab (i.e. it does not reflect all patients currently on omalizumab). It is estimated that 2,200 patients are currently on omalizumab therapy (irrespective of whether they are eligible for mepolizumab or not). It is estimated from IDEAL[23] that [redacted] of mepolizumab eligible patients are also eligible for add-on omalizumab.

Table 158 Estimated market share and associated patient numbers with and without mepolizumab

	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
With no mepolizumab					
SoC	15,520 96%	15,450 95%	15,298 93.5%	15,142 92%	14,902 90%
Add-on omalizumab	647 4%	813 5%	1,063 6.5%	1,317 8%	1,656 10%
With the introduction of mepolizumab					
SoC	15,439 95.5%	15,206 93.5%	14,807 90.5%	13,990 85%	12,915 78%
Add-on omalizumab	647 4%	813 5%	982 6%	1,152 7%	1,325 8%
Add-on mepolizumab	81 0.5%	244 1.5%	573 3.5%	1,317 8.0%	2,318 14%

6.3 In addition to technology costs, please consider other significant costs associated with treatment that may be of

interest to commissioners (for example procedure codes and programme budget planning)?

In addition to medication costs the budget impact model also incorporates the administration costs and all relevant costs associated with these technologies (derived from the economic model). For mepolizumab and omalizumab this includes routine visits (face-to-face appointments with a respiratory consultant), administration costs (time of a specialist nurse to administer biologic therapy) and monitoring costs (specialist nurse time to monitor patients post biologic treatment administration). All costs are taken from the economic model (refer to Section 5.5.2 and 5.5.3). As outlined in Section 2.4 no additional tests or investigations are necessary to identify the population for whom mepolizumab is indicated in the marketing authorisation. Severe asthma patients are already phenotyped in a specialist setting. A blood test for eosinophil levels is required to identify those patients most likely to respond to mepolizumab and this already forms part of the routine assessment of patients during screening for severe asthma. Appropriate facilities already exist for the administration of omalizumab (a biologic for severe persistent allergic, IgE driven asthma; see section 3.3). However, increased capacity as a result of increasing demand from patients deemed eligible for mepolizumab may need to be addressed locally.

6.4 What unit costs were assumed? How were these calculated? If unit costs used in the health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Treatment costs (list price in the budget impact calculation – please refer to the confidential addendum to this submission for a budget impact summary based on PAS prices) are derived from the economic model; cost inputs are described in detail in Section 5.5.

6.5 Were there any estimates of resource savings? If so, what were they?

By reducing the number of clinically significant exacerbations, mepolizumab provides resource savings associated with treating exacerbations. As shown in Section 5.7 over a life time horizon this is estimated to provide a saving of [redacted] versus SoC alone in the GSK proposed population. However, for simplicity, savings associated with exacerbations are not included in this budget impact calculation.

There are other resource use savings that mepolizumab offers which are not captured here:

- Compared to omalizumab, testing for eosinophil levels predictive of response is cheap (full blood test) and already forms part of a patient's assessment. Conversely the IgE test required for omalizumab is not routine and associated with a higher (unknown) cost.

- The long term cost savings associated with patients reducing or stopping maintenance OCS and the health consequences of doing so such as cataract, MI, osteoporosis etc.

6.6 What is the estimated budget impact for England and Wales?

Committee members are asked to refer to the confidential addendum to this submission to provide a more realistic estimate of the budgetary impact of mepolizumab. Table 159 shows the estimated budget impact to the NHS of introducing mepolizumab, assuming positive NICE guidance in GSK's proposed patient population. Note that mepolizumab is an add-on cost to SoC alone and a possible displacement cost versus omalizumab. Based on list prices for both mepolizumab and omalizumab, the budget impact of introducing mepolizumab is estimated at £906,674 in year 1 rising to £22.8M in year 5 (£45.4M cumulative budget impact).

Table 159 Estimated budget impact of introducing add-on mepolizumab – List price applied for mepolizumab and omalizumab.

Cost	Year 1	Year 2	Year 3	Year 4	Year 5
Current situation without add-on mepolizumab					
SoC Acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Add-on omalizumab Acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**£23,563,714**	**£25,150,465**	**£27,645,709**	**£30,394,976**	**£33,947,278**
With the introduction of mepolizumab					
SoC Drug Acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Add-on omalizumab Drug Acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Add-on mepolizumab Drug Acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Total	**£24,470,388**	**£27,880,193**	**£33,373,562**	**£43,617,799**	**£56,767,947**
Budget impact					
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**£906,674**	**£2,729,729**	**£5,727,852**	**£13,222,823**	**£22,820,670**
Cumulative total	**£906,674**	**£3,636,403**	**£9,364,255**	**£22,587,078**	**£45,407,748**

Monitoring costs include: routine appointments, administration and monitoring.

The ERG and NICE Committee are asked to refer to the confidential addendum to review the resultant budget impact with the application of PAS prices.

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Single technology appraisal

Mepolizumab for treating severe eosinophilic asthma [ID798]

Dear Claire and Christoph,

The Evidence Review Group, ScHARR Technology Assessment Group, and the technical team at NICE have looked at the submission received on 23 November 2015 from GSK. The ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on 7 January 2016. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Helen Tucker, Technical Lead (Helen.Tucker@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Melinda Goodall
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

Literature searching

A1. In Appendices 8.2, 8.9, 8.12, 8.13, 8.14 of the company's submission filters to identify RCTs and observational studies have been used in the clinical effectiveness searches; and various filters have been used in the searches related to cost effectiveness, resource use and utilities. Please specify whether published, validated filters have been used and give details of any alterations made.

Systematic Review methods

A2. The NICE scope includes the following outcomes that are not included in the company's list of inclusion criteria for the systematic review (Table 6).

a. patient and clinician evaluation of response
b. mortality
c. time to discontinuation

Please clarify if studies including just these outcomes may have been excluded from the review.

A3. Page 156 of the company's submission: Please provide a reference and a rationale for the quality assessment tool that has been used.

A4. Table 96, page 181 of the company's submission: Please clarify why systematic searches about asthma mortality were only included in the cost effectiveness review. Please comment on the likely impact of asthma mortality not being included in the clinical effectiveness review, including whether any relevant information might have been excluded such as data from The National Review of Asthma Deaths (NRAD)

Data analyses

A5. **Priority Question:** Please provide clinical data (including clinically significant exacerbations, hospitalisations and quality of life (QoL)) for the subgroup of patients that constitute the additional patients in the company's proposed population. That is, "Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/μL at initiation of treatment and dependency on systemic corticosteroids with <4 exacerbations in the previous year". Please provide this data from the DREAM, MENSA and SIRIUS trials separately, and as a meta-analysis, including SIRIUS data as a sensitivity analysis.

A6. **Priority Question:** Clinical advisors to the ERG suggest that the selection of patients with ≥300 cells/μL in the previous 12 months, instead of ≥150 cells/μL at initiation of treatment, is more clinically relevant for the identification of eosinophilic patients.

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Table 44 on page 103 of the company's submission shows that patients with ≥300 cells/μL in the previous 12 months in the placebo groups have fewer exacerbations on average than patients with <300 cells/μL (1.64 versus 1.89). Further, the rate ratios for patients with ≥300 cells/μL in the previous 12 months are less favourable than for patients with <300 cells/μL. Please comment on these results.

A7. **Priority Question.** Please provide the efficacy data for the SIRIUS population with ≥4 exacerbations per year. It is acknowledged that there may be large uncertainty due to small patient numbers (as noted on page 83 of company's submission) but the ERG are of the opinion that this analysis is feasible.

A8. Please provide analyses (clinically significant exacerbations, hospitalisations and QoL) for patients with:

a. ≥300 cells/μL in the previous 12 months,

b. in the company's proposed population, and

c. in the company's proposed population excluding patients on maintenance oral corticosteroids (mOCS) with <4 exacerbations in the previous year.

A9. Please provide tables of clinical outcome data (including clinically significant exacerbations, hospitalisations and QoL) for each study with the original ITT populations and the two company proposed populations side by side.

A10. Section 4.4 pages 53-59 of the company's submission: Missing data due to patient withdrawals were analysed using a Missing at Random assumption for DREAM and MENSA, with two sensitivity analyses performed (Table 13, page 59). Please provide further information on the methods and key findings of these analyses. Please also clarify the findings for the sensitivity analysis performed for missing data in SIRIUS.

A11. Please clarify whether the difference between study groups in the number of exacerbations that require hospitalisations in the preceding year in MENSA are theoretically likely to impact on the observed results. For information, in the company's proposed population (calculated from Table 17): 13% of the placebo arm had 3 or more exacerbations compared with 2% in the mepolizumab 75mg IV arm and 6% in the mepolizumab 100mg SC arm.

A12. Page 167 of the company's submission: Please provide additional details about the systemic reactions and hypersensitivity reactions, including the comparative data between placebo and mepolizumab arms, the seriousness of the events, and any sequelae. Please provide tables detailing the "adverse events of special interest" for the key efficacy trials and for the open label extension trials.

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A13. Please provide the rate of hospitalisations results alone for SIRIUS in the company's proposed population and ITT population.

A14. Section 4.7.3.1 Figure 7, page 77 of the company's submission: The submission illustrates the threshold of eosinophil blood count that predicts a 30% reduction in the rate of exacerbation using a modelling concept. Please provide details of the models used to produce Figure 7.

A15. Page 107 of the company's submission: It is stated that in DREAM the "interaction between the number of previous exacerbations and treatment group was potentially significant (p=0.014)". Please provide details of the threshold of eosinophil blood count that predicts a 30% reduction in the rate of exacerbation, separately conditional upon the number of previous exacerbations.

A16. Section 4.7.3.1 Figure 8 and Table 22, page 79 of the company's submission. Please clarify details of the modelling procedure. Specifically, do the results in Figure 8 reflect those that are presented in Table 22, including correction for the same covariates?

Study design

A17. **Priority Question.** Regarding the MENSA and SIRIUS trials, please clarify what led to patients withdrawing during the run-in periods. Please also clarify what the continuation criteria were in MENSA (page 62 – 63 of the company's submission) and SIRIUS (Page 46 and page 65 of the company's submission). Please provide the baseline characteristics of the patients who met the initial eligibility criteria but were not enrolled in the trial (that is, those lost during the run-in phase), preferably in tables alongside patients who were enrolled. Please comment on how this might impact on the generalisability of the MENSA and SIRIUS trial efficacy estimates to clinical practice?

A18. Please clarify why 9 patients in the DREAM trial were withdrawn at the "investigator's discretion" (Patient flow, Page 61 of the company's submission).

A19. Please clarify whether the continuation rules for treatment with mepolizumab in COSMOS and COLUMBA were consistent with the recommendations in the SmPC for mepolizumab. (Page182 of the company's submission) Please clarify if the continuation rules in these trials differ from the continuation rule used in the company's economic model.

A20. Please clarify the definition of standard care used in each of the omalizumab and mepolizumab trials, including details of the treatments given.

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A21. Please clarify why patients in COSMOS and COLUMBA were only selected if they continued with controller therapy (page 151 of the company's submission) and what type of controller therapy was eligible?

A22. Please clarify whether the company expect that monitoring (i.e. of all patients being given mepolizumab) or measuring (e.g. where response to therapy has decreased in a given patient) of antibody resistance will be necessary in patients in clinical practice?

Meta-analyses

A23. **Priority Question.** Please provide baseline and efficacy data for DREAM in the company's proposed population and ITT populations, for each study arm.

A24. **Priority Question.** Please provide a meta-analysis of MENSA and DREAM (page 114 of the company's submission) compared with standard of care in the company's proposed population, and in the proposed population excluding maintenance oral corticosteroids (mOCS) users. Please provide these analyses for all outcomes (including clinically significant exacerbations, hospitalisations and QoL). Please also provide a sensitivity analysis including SIRIUS.

A25. Section 4.9.3.1 of the company's submission. Please clarify whether the numbers, specifically the meta-analysis numbers, are correct throughout this section. For example:

a. Table 54, pg122-123. Mepolizumab 75mg IV has a rate ratio (RR) of 0.40 for DREAM and mepolizumab 75mg IV/100 mg subcutaneous has a RR of 0.52 for MENSA. The combined RR for these groups is given as 0.53. In Figure 17, pg. 114 the RR for this combined group is given as 0.46.

b. Table 55, mepolizumab 75mg IV has Rate Ratios of 0.61 for both DREAM and MENSA but a combined rate ratio of 0.57. Further, clarify why for mepolizumab 100mg subcutaneous is blank for DREAM & MENSA, rather than containing the MENSA results.

Network meta-analysis

A26. Please clarify what the inclusion/exclusion criteria were for the network meta-analysis, presented in a table using the PICOS format. Please include a rationale for the criteria used.

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Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** Please provide an individual ICER for the group of patients that constitute the additional patients in the company's proposed population. That is, "Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/μL at initiation of treatment and dependency on systemic corticosteroids with <4 exacerbations in the previous year". At present this ICER is obscured by the aggregation of the two populations.

B2. **Priority Question.** Please provide an analysis of patients in the SIRIUS ITT population and estimate the threshold level of QALYs that would be required from reduced oral corticosteroid use for the ICER to be £20,000 per QALY and £30,000 per QALY.

B3. **Priority Question.** Please clarify the ICER for mepolizumab using only the data from the 100mg subcutaneous groups.

B4. **Priority Question.** Please clarify why the exacerbation rates from COLUMBA and COSMOS were not used for the long-term extrapolation data for mepolizumab. Please provide an analysis assessing the impact on the ICER of using these values.

B5. **Priority Question.** Please clarify how the annual exacerbation rate is calculated for those meeting mepolizumab's continuation criteria. The assumed number (0.645, Transitions!AD17 in the model) for those meeting the criteria in the company's proposed population is markedly lower than that for all patients in this population (1.206, Transitions!AD14 in the model) despite 92.3% of the patients meeting the criteria.

B6. **Priority Question.** Please provide an analysis assessing the impact on the ICER using the meta-analysis of MENSA and DREAM on the company's proposed population and the company's proposed population excluding mOCS users.

B7. **Priority Question.** Please clarify whether the continuation rule assumed in the model (that is, patients continue unless they worsen) has been proposed elsewhere (e.g. guidelines). If possible, provide exploratory analyses to assess the impact on the ICER of varying the continuation rule, that is assuming patients had to have improved by a certain amount (as gauged by reduction of exacerbations or OCS use).

B8. If possible, please provide the ICERs that would be generated using the populations requested in question A9.

B9. Please clarify how mapping from the SGRQ to the EQ-5D would resolve the fundamental problems of using the EQ-5D in asthma that were stated by the company in section 5.4.1 of the submission.

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B10. If possible, please clarify how the answer to A12 would qualitatively affect the ICER.

B11. Given the increased risk of mortality following hospitalisation as age increases observed in Roberts 2013, (0.0045 between 45 and 54 and a rate of 0.0278 at 65 years and over) please provide a rationale for grouping all patients aged 45 and over and assuming one rate of mortality. If possible, please provide exploratory analyses to assess the impact on the ICER of increased rates of mortality by age that would be consistent with the data presented in Watson 2007.

B12. Please provide the ICER if the mapped utility were used but no other disutilities from exacerbation or hospitalisations were applied. This would provide a bound on the impact of double counting of adverse events.

B13. Please clarify why the exacerbation rate for patients not meeting the continuation criteria is not calculated from the MENSA trial but rather assumes the same exacerbation rate as for SoC. Please provide the ICER were the MENSA data used instead.

B14. Please clarify why the 0.004 annual asthma mortality rate reported by de Vries 2010 was assumed to equal the mortality rate following an exacerbation?

B15. Please clarify what evidence is available to support the assumption that the proportion of patients meeting the continuation criteria at 32 weeks (from the MENSA trial) would be maintained at 52 weeks.

Section C: Textual clarifications and additional points

C1. Page 15. Please clarify the meaning of a “like-NICE” approach?

C2. Table 6 page 31. There are two asterisks. Please clarify if “**” in the table relates to footnote *** If this is the case, please clarify what the second footnote denoted “*” relates to?

C3. Table 14 page 62. Please confirm that the figures in column 3 (75mg) - it states 129 (84%) completed, and 130 (85%) entered the follow-up phase - are correct.

C4. Table 36 page 95. Please clarify the estimate for the RR of Mepolizumab 75 mg IV for exacerbations requiring hospitalisation/ED visits, as the current estimate falls outside of the confidence interval.

C5. Table 27 page 32. There is no footnote 3. Please clarify whether this starts at the second “Note:”?

C6. Page 115. It is stated “trend confirmed by reduced times to first exacerbation”. Please clarify if this should be “increased time to first exacerbation”?

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C7. Page 142. Please check and clarify whether the reference to Table 63 should be to Table 67. Also “Table 67 and 68” on page 143 should be 68 and 69? Tables 64 and 65 on page 146 should refer to Tables 72 and 73?

C8. Page 132/133. Please clarify what is the “population feasibility” section referred to in the table footnote?

C9. Table 97 page 185. Table from Sonathi et al onwards – the data appears to be in the wrong columns. Please provide a corrected table.

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12th January 2015

Dear Melinda and Jeremy,

Thank you for sending the clarification questions from the Evidence Review Group, ScHARR Technology Assessment Group, and the technical team at NICE on Friday 11 December and Tuesday 15 December 2015 regarding the appraisal document for mepolizumab in severe refractory eosinophilic asthma (ID798) submitted on 19 November 2015.

A written response is provided and as requested commercial in confidence (CIC) and academic in confidence (AIC) is highlighted appropriately. Confidential information is listed in the check list.

A second document is provided which removes all the CIC and AIC information.

Should you have any queries with the provided responses please contact Helen Starkie Camejo (helen.j.starkie-camejo@gsk.com).

Many thanks.

Kind regards,

Helen and Christoph

Dr Helen Starkie Camejo – Programme Lead, Health outcomes, Respiratory
Dr Christoph Hartmann – Senior Medical Adviser

Section A: Clarification on effectiveness data AND Additional clarification questions

Literature searching

A1. In Appendices 8.2, 8.9, 8.12, 8.13, 8.14 of the company's submission filters to identify RCTs and observational studies have been used in the clinical effectiveness searches; and various filters have been used in the searches related to cost effectiveness, resource use and utilities. Please specify whether published, validated filters have been used and give details of any alterations made.

All systematic reviews were conducted by experienced systemic literature reviewers. The search strings are based on our usual list of search terms/strings for the topics (RCTs, observational, economic, etc) and crosschecked with the NICE appraisal document of omalizumab especially for comparators/compounds in this indication.

Systematic Review methods

A2. The NICE scope includes the following outcomes that are not included in the company's list of inclusion criteria for the systematic review (Table 6).

a. patient and clinician evaluation of response
b. mortality
c. time to discontinuation

Please clarify if studies including just these outcomes may have been excluded from the review.

All three outcomes were captured in the systematic literature review of clinical effectiveness.

a. patient and clinician evaluation of response
Patient and clinician evaluation of response is captured in Table 6 under *Outcomes*, as part of bullet point *Efficacy*. In the systematic review report this is captured under '*Response to treatment*'. For RCTs, refer to Section 3.2, page 56 and for non-RCTs, Section 4.2, page 153.

b. mortality
Mortality is captured under *Outcomes* in Table 6 as part of S*afety and tolerability*. Specifically in the systematic review report, mortality is reported in Section 3.8 *Withdrawal rates* on page 114.

c. *time to discontinuation*
Time to discontinuation is captured under *Outcomes* in Table 6 as part of *Safety and tolerability*. Specifically in the systematic review report, time to discontinuation is reported in Section 3.8 *Withdrawal rates* on page 114 (captured as with withdrawal or discontinuation rates).

Therefore no studies should have been inadvertently excluded based on these outcomes.

A3. Page 156 of the company's submission: Please provide a reference and a rationale for the quality assessment tool that has been used.

Page 156 provides the quality assessment tool applied to non-RCTs. The tool for the quality assessment of the non-RCTs was identified and adapted from Centre for Reviews and Dissemination (CRD) (2008) Systematic reviews, CRD's guidance for undertaking reviews in health care. This is the same tool used to assess non-RCTs identified through the systematic literature review of clinical effectiveness (refer to the Systematic Literature Review Report for Clinical Effectiveness, page 30).

A4. Table 96, page 181 of the company's submission: Please clarify why systematic searches about asthma mortality were only included in the cost effectiveness review. Please comment

on the likely impact of asthma mortality not being included in the clinical effectiveness review, including whether any relevant information might have been excluded such as data from The National Review of Asthma Deaths (NRAD)

As per our answer to A2, mortality was included in the systematic review of clinical effectiveness. However, in addition to this, since mortality was deemed as a key driver of the cost-effectiveness in the NICE MTA of omalizumab, we felt mortality warranted a separate systematic search with the economic model in mind.

Something such as the NRAD report would not have been captured by the systematic review of clinical effectiveness given a number of factors such as relevant patient population (overall broader asthma patient population), absence of intervention and comparator etc.

Inspection of the inclusion criteria for the mortality systematic literature review included only a severe asthma population and therefore the NRAD report would not have been picked up in these searches either.

As described in the main submission, on page 202 (Section 5.3.6 Mortality), NRAD was identified through hand searching. However, to offer some degree of reassurance that other more appropriate sources of mortality were not missed, NRAD is the first UK wide study of asthma deaths and the largest worldwide study of this kind to date.

Data analyses

A5. Priority Question: Please provide clinical data (including clinically significant exacerbations, hospitalisations and quality of life (QoL)) for the subgroup of patients that constitute the additional patients in the company's proposed population. That is, "Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/μL at initiation of treatment and dependency on systemic corticosteroids with <4 exacerbations in the previous year". Please provide this data from the DREAM, MENSA and SIRIUS trials separately, and as a meta-analysis, including SIRIUS data as a sensitivity analysis.

Table 1 shows the requested data for 'Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/μL at initiation of treatment and dependency on systemic corticosteroids with <4 exacerbations in the previous year'. In the requested analysis the patient numbers were very low, with numbers being between 15 to 30 subjects per arm, making it difficult to draw conclusions.

Overall, as expected and discussed in the main submission (section 4.7 and 4.13) patients on maintenance OCS with <4 exacerbations showed less clinical benefit than the proposed patient population (Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/μL at initiation of treatment, with ≥4 exacerbations in the previous year or dependency on systemic corticosteroids with <4 exacerbations in the previous year). It is important to consider that, from a clinical perspective, patients on maintenance OCS with less than 4 exacerbations in the previous year are able to experience an additional clinical benefit from a reduction in OCS use, and thus it is a major therapy objective of add-on mepolizumab therapy. In SIRIUS the odds of patients reducing their OCS dose was 2.39 for mepolizumab vs. SOC (ITT, 95% CI 1.25 – 4.56, p=0.008, Section 4.7.5.6 of main submission).

The main benefit of a reduction in OCS is the decreased burden of short- and long-term side effects of systemic corticosteroids. However, this benefit is difficult to capture in clinical trials and indeed patients receiving OCS show benefit in terms of asthma control, including a reduction in exacerbations. Thus, while add-on therapy with mepolizumab reduces the need for OCS, the incremental benefit in terms of asthma control may have been masked by the impact of the OCS treatment. This trend is evident in the ITT population results in MENSA; 100mg SC mepolizumab reduced exacerbation rate of non-OCS users by 66% (RR 0.34, 95% CI 0.23, 0.51) versus 20% (RR 0.80, 95% CI 0.49, 1.29) in OCS users (Table 46, Section 4.8.1.5 of main submission).

Nonetheless, in patients on maintenance OCS with less than 4 exacerbations in the previous year, clinician's feedback was clear, that a reduction in systemic corticosteroid exposure while maintaining asthma control was an additional major therapy objective of add-on mepolizumab therapy. We therefore also propose to include those patients dependent on maintenance OCS in the company's proposed population irrespective of exacerbation history.

The results in the table below have to be assessed with caution due to potential high variability in the results, deemed by the small numbers of subjects. While, overall the results show a trend that supports our discussion above, we believe that the clinical benefits in this patient group have not been captured fully due to the difficulty in measuring the impact of OCS reduction and in addition it would be inequitable to exclude this more severe patient population from the potential to benefit from mepolizumab therapy.

Please see A24 (below) for results and discussion of the meta-analysis results.

Table 1: Clinical data for patients with ≥ 150 cells/µL and <4 exacerbation in the past year and on maintenance OCS treatment

		Subjects with ≥ 150 cells/µL Baseline Blood Eosinophils and <4 Exacerbations in the past year and Baseline Maintenance OCS use								
		DREAM				MENSA			SIRIUS	
		Pbo	75mg IV	250mg IV	750mg IV	Pbo	75mg IV	100mg SC	Pbo	100mg SC
Rate of Clinically Significant Exacerbations	N	**24**	**15**	**22**	**17**	**19**	**17**	**24**	**33**	**32**
	Exacerbation rate/year	2.8	1.15	1.15	1.24	1.4	0.63	1.3	2.05	1.54
Comparison vs placebo	Rate ratio		**0.41**	**0.41**	**0.44**		**0.45**	**0.93**		**0.75**
	95% CI		0.19, 0.86	0.21, 0.79	0.22, 0.90		0.16, 1.24	0.42, 2.03		0.44, 1.29
	p value		0.019	0.008	0.024		0.121	0.855		0.298
Rate of Exacerbations requiring Hospitalisation or ED visits	N	**24**	**15**	**22**	**17**	**19**	**17**	**24**	**33**	**32**
	Exacerbation rate/year	0.7	0.33	0.23	0.19	0.23	0.25	0.06	0.17	0.1
Comparison vs placebo	Rate ratio		**0.47**	**0.32**	**0.27**		**1.1**	**0.25**		**0.59**
	95% CI		0.09, 2.62	0.06, 1.65	0.04, 1,73		0.21, 5.86	0.03, 2.49		0.09, 3.71
	p value		0.391	0.174	0.167		0.909	0.239		0.572
Rate of Exacerbations requiring Hospitalisation	N	**24**	**15**	**22**	**17**	**19**	**17**	**24**	**33**	**32**
	Exacerbation rate/year	0.65	0.21	0.25	0.08	0.07	0.07	0.07	Insufficient events to perform analysis[1]	
Comparison vs placebo	Rate ratio		**0.33**	**0.37**	**0.11**		**0.98**	**0.96**		
	95% CI		0.04, 2.99	0.06, 2.47	0.01, 1.67		0.06, 16.60	0.06, 16.84		
	p value		0.321	0.308	0.113		0.986	0.979		
SGRQ	N	**SGRQ was not an endpoint in DREAM**				**19**	**16**	**22**	**30**	**29**
	LS Mean (SE)					38.1 (3.38)	35.4 (3.69)	36.9 (3.17)	43.0 (2.24)	37.2 (2.28)
	LS Mean Change (SE)					-10.7 (3.38)	-13.4 (3.69)	-11.9 (3.17)	-1.7 (2.24)	-7.5 (2.28)
Comparison vs placebo	Difference						**-2.7**	**-1.2**		**-5.8**
	95% CI						-12.8, 7.5	-10.8, 8.4		-12.3, 0.7
	p value						0.602	0.803		0.08
ACQ	N	**20**	**13**	**19**	**16**	**18**	**16**	**22**	**Analysis did not converge[2]**	
	LS Mean (SE)	1.90 (0.268)	1.91 (0.341)	1.36 (0.291)	1.57 (0.305)	1.86 (0.196)	1.56 (0.208)	1.38 (0.180)		
	LS Mean Change (SE)	-0.56 (0.268)	-0.55 (0.341)	-1.11 (0.291)	-0.89 (0.305)	-0.55 (0.196)	-0.85 (0.208)	-1.04 (0.180)		
Comparison vs placebo	Difference		**0.01**	**-0.54**	**-0.33**		**-0.3**	**-0.48**		
	95% CI		-0.81, 0.84	-1.29, 0.20	-1.13, 0.47		-0.87, 0.28	-1.03, 0.07		
	p value		0.972	0.148	0.407		0.304	0.083		
EQ-5D	N	**20**	**14**	**20**	**16**	**EQ-5D was not an endpoint in MENSA and SIRIUS**				
Week 52 Index score	Mean (SD)	0.75 (0.287)	0.86 (0.141)	0.83 (0.189)	0.82 (0.184)					
	Median	0.82	0.83	0.87	0.8					
	Min, Max	0.1, 1.0	0.6, 1.0	0.5, 1.0	0.5, 1.0					
Week 52 Change from Baseline	n	**20**	**14**	**20**	**16**					
	Mean (SD)	0.00 (0.243)	0.07 (0.179)	0.10 (0.197)	0.13 (0.2)					
	Median	0	0.03	0.02	0.04					
	Min, Max	-0.5, 0.4	-0.3, 0.3	-0.2, 0.6	-0.1, 0.5					

1. For exacerbations requiring ER visits/ hospitalisations in SIRIUS there were only 3 patients in the mepolizumab arm in the overall population who had these events and even fewer in the subgroup analysis. No patient suffered more than one of these events in the mepolizumab arm. This meant that there was insufficient data to fit a "rate of exacerbations" for this endpoint for the mepolizumab group. For exacerbations requiring hospitalisation, no patients in the mepolizumab arm in the overall population had one of these events so there was even less information.
2. ACQ was measured on a weekly basis in SIRIUS. Therefore, the analysis was fitted with a model which estimated the effects separately at each visit, and for the subgroup analysis this failed to converge since the number of visits was large relative to the number of subjects.

A6. Priority Question: Clinical advisors to the ERG suggest that the selection of patients with ≥300 cells/μL in the previous 12 months, instead of ≥150 cells/μL at initiation of treatment, is more clinically relevant for the identification of eosinophilic patients. Table 44 on page 103 of the company's submission shows that patients with ≥300 cells/μL in the previous 12 months in the placebo groups have fewer exacerbations on average than patients with <300 cells/μL (1.64 versus 1.89). Further, the rate ratios for patients with ≥300 cells/μL in the previous 12 months are less favourable than for patients with <300 cells/μL. Please comment on these results.

We agree with the clinicians that historic eosinophil counts with ≥300 cells/μL are more relevant in the identification (i.e. diagnosis) of eosinophilic asthma. For clarity, all patients in the phase IIb/III clinical trials had to fulfil diagnostic criteria of severe refractory eosinophilic asthma before entering the trials as outlined in the RCT CSRs. The company's proposal for the selection of patients with eosinophil count of ≥150 cells/μL at initiation of treatment is not intended for diagnosis but as a predictor of response to mepolizumab.

The selected eosinophil threshold of ≥150 cells/μL at initiation of treatment is intended to identify those severe refractory eosinophilic asthma patients that are likely to receive a clinical benefit from mepolizumab. Specifically, using this eosinophil threshold, add-on mepolizumab has demonstrated clinically meaningful benefits in patients with severe refractory eosinophilic asthma such as a reduction in the rate of exacerbations by ≥30% (Figure 7, page 77 of main submission).

In the clinical trials, the selection of ≥300 cells/μL in the previous 12 months was also investigated as a predictor of response to add-on mepolizumab therapy in the already diagnosed severe refractory eosinophilic asthmatic. The results showed that using ≥300 cells/μL in the previous 12 months as a marker was a less sensitive predictor to mepolizumab response compared to ≥150 cells/μL at initiation of treatment. When appraising table 44 in the main submission it has to be noted that patients that did not fulfil the ≥300 cells/μL in the previous 12 months (i.e. with <300 cells/μL) still fulfilled the selection criterion of ≥150 cells/μL at initiation of treatment.

Rationale for why ≥150 cells/μL at initiation of treatment is a better predictor of response to mepolizumab add-on therapy than ≥300 cells/μL in the previous 12 months have been presented in the main submission (Table 44). Patients with severe refractory eosinophilic asthma and ≥150 cells/μL at initiation of treatment (i.e. including those with <300 cells/μL in the previous 12 months) showed a bigger reduction in rate of exacerbations compared to patients that were included based on ≥300 cells/μL in the previous 12 months. Table 20 on page 78 of the main submission further supports this rationale where a clinically significant reduction in rate of exacerbation can be observed in the patients entering the trial based on an eosinophil count of 150 cells/μL at initiation of treatment (52% reduction in the 100mg SC arm) compared to a non-clinically significant reduction in rate of exacerbations observed in patients that were selected based on a eosinophil count of ≥300 cells/μL in the previous 12 months (18% reduction in the 100mg SC arm).

In defining our strategy for this submission and being mindful of an efficient use of NHS resources, we were seeking to identify a population with an enhanced potential for clinical benefit and hence was more likely to justify positive NICE guidance. Utilising the count of ≥150 cells/μL at initiation of treatment gave an enhanced clinical benefit vs. historical eosinophil levels of ≥300 cells/μL in the previous 12 months. Thus, ≥150 cells/μL at initiation of treatment is more likely to identify those with enhanced capacity to benefit and was therefore used to identify our target population.

A7. Priority Question. Please provide the efficacy data for the SIRIUS population with ≥4 exacerbations per year. It is acknowledged that there may be large uncertainty due to small patient numbers (as noted on page 83 of company's submission) but the ERG are of the opinion that this analysis is feasible.

Please see the results Table 2 in A9. As previously mentioned the number of SIRIUS patients that fulfilled the inclusion criteria of ≥150 cells/μL in addition to ≥4 exacerbations was small (15 and 22 in the placebo and 100mg SC arms, respectively). Thus, results from this analysis should be reviewed in light of the high uncertainties.

Overall there is a similar trend in reduction of maintenance OCS dose compared to the ITT population (ITT OR 2.39, p=0.008 vs GSK proposed population excluding <4 exacerbations per year OR 2.75, p=0.140), this was true for the overall odds ratio, and for achieving a 50% reduction in OCS dose, to less than 5mg/day and for the median percentage reduction in daily OCS usage (see table 2, section A9). For other endpoints, including rate of exacerbation and SGRQ the GSK proposed population excluding <4 exacerbations in the last year matched the trend seen in the ITT population. Due to insufficient events no analysis of ED visits and/or hospitalisation could be performed.

As expected and discussed in the main submission, when excluding those patients with less than 4 exacerbations from the proposed population, thus selecting a more severe patient population, a slight improvement in outcome is observed compared to when including those on maintenance OCS with less than 4 exacerbation in the last year (the GSK proposed population). However, the GSK proposed population still benefits from the reduction in OCS burden whilst maintaining and improving their asthma control, which is reflected in their statistically and clinically meaningful improvements in quality of life (SGRQ) and asthma control (ACQ). Including patients on maintenance OCS with less than 4 exacerbations in the reimbursement population will ensure that those patients with an increased burden of significant OCS side effects due to their asthma severity can benefit from add-on mepolizumab therapy.

In addition, we are concerned that excluding these more severe patients could result in guidance where it would be only possible for them to be eligible for treatment if their OCS was withdrawn and they began to exacerbate more frequently again, with the potential to put patients at significant risk. Therefore, including patients on maintenance OCS with less than 4 exacerbations in the reimbursement population is ethical and equitable for patients.

A8. ~~Please provide analyses (clinically significant exacerbations, hospitalisations and QoL) for patients with:~~

~~a. ≥300 cells/μL in the previous 12 months,~~

~~b. in the company's proposed population, and~~

~~c. in the company's proposed population excluding patients on maintenance oral corticosteroids (mOCS) with <4 exacerbations in the previous year.~~

Revised on clarification:
A8 in the clarification letter should be as follows:

A8 Please provide analyses (clinically significant exacerbations, hospitalisations and QoL) for patients with:

d. ≥300 cells/μL in the previous 12 months in the company's proposed population,

e. and in the company's proposed population excluding patients on maintenance oral corticosteroids (mOCS) with <4 exacerbations in the previous year.

This analysis is not available. However, for the reasons stated in the answer to A6, we conclude that using ≥150 cells/μL at initiation of treatment is a more robust marker of response to add-on

mepolizumab therapy compared to ≥300 cells/μL in the previous 12 months. Please see answer A6 for rational why analysis is not provided.

A9. Please provide tables of clinical outcome data (including clinically significant exacerbations, hospitalisations and QoL) for each study with the original ITT populations and the two company proposed populations side by side.

Below we provide clinical outcomes with the original ITT populations and the two company proposed populations side by side for all RCTs (please see Table 2). Please note that the primary endpoints were different for DREAM and MENSA (frequency of clinically significant exacerbations) compared to SIRIUS (percent reduction of OCS dose). Furthermore, DREAM included patients selected based on fulfilling 1 of 4 inclusion criteria (blood eosinophil count, sputum eosinophil count, FeNO, or deterioration following maintenance medication reduction; please see page 41 & 42 of main submission for full details) compared to MENSA and SIRIUS, which selected patients on criteria identified in DREAM to have increased benefit from add-on mepolizumab therapy (severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/μL at initiation of treatment or ≥300 cells/μL in the previous 12 months). Thus, a direct comparison of endpoints between the individual studies has to be performed in the context of these differences in study design.

Table 2: Clinical outcome data (DREAM, MENSA and SIRIUS, ITT Population and Proposed Populations)

		DREAM												MENSA									SIRIUS					
		ITT				GSK Proposed Population excluding mOCS users with <4 exacerbations				GSK Proposed Population				ITT			GSK Proposed Population excluding mOCS users with <4 exacerbations			GSK Proposed Population			ITT		GSK Proposed Population excluding mOCS users with <4 exacerbations		GSK Proposed Population	
		Pbo	75mg IV	250mg IV	750mg IV	Pbo	75mg IV	250mg IV	750mg IV	Pbo	75mg	250mg IV	750mg IV	Pbo	100mg SC	75mg IV	Pbo	100mg SC	75mg IV	Pbo	100mg SC	75mg IV	Pbo	100mg SC	Pbo	100mg SC	Pbo	100mg SC
Rate of Clinically Significant Exacerbations	n	155	153	152	156	32	39	29	34	56	54	51	51	191	194	191	45	54	48	64	78	65	66	69	15	22	48	54
	Exacerbation rate/year	2.4	1.24	1.46	1.15	3.64	1.13	0.91	1.11	3.08	1.12	0.96	1.13	1.74	0.83	0.93	3.1	1.22	1.2	2.65	1.32	1.06	2.12	1.44	2.16	1.75	2.1	1.62
Comparison vs placebo	Rate ratio		**0.52**	**0.61**	**0.48**		**0.31**	**0.25**	**0.31**		**0.36**	**0.31**	**0.37**		**0.47**	**0.53**		**0.39**	**0.39**		**0.5**	**0.4**		**0.68**		**0.81**		**0.77**
	95% CI		0.39, 0.69	0.46, 0.81	0.36, 0.64		0.18, 0.53	0.14, 0.45	0.18, 0.53		0.24, 0.55	0.20, 0.48	0.24, 0.57		0.35, 0.64	0.40, 0.72		0.23, 0.67	0.22, 0.68		0.32, 0.78	0.24, 0.67		0.47, 0.99		0.40, 1.64		0.51, 1.17
	p value		<0.001	<0.001	<0.001		<0.001	<0.001	<0.001		<0.001	<0.001	<0.001		<0.001	<0.001		<0.001	<0.001		0.002	<0.001		0.042		0.556		0.222
Rate of Exacerbations requiring Hospitalisation or ED visits	n	155	153	152	156	32	39	29	34	56	54	51	51	191	194	191	45	54	48	64	78	65	66	69	15	22	48	54
	Exacerbation rate/year	0.43	0.17	0.25	0.22	0.56	0.16	0.17	0.22	0.63	0.21	0.21	0.23	0.2	0.08	0.14	0.59	0.26	0.12	0.52	0.26	0.16	0.22	0.08	**Due to insufficient events no analysis could be performed**		0.2	0.07
Comparison vs placebo	Rate ratio		**0.4**	**0.58**	**0.52**		**0.29**	**0.31**	**0.40**		**0.33**	**0.33**	**0.36**		**0.39**	**0.68**		**0.45**	**0.21**		**0.49**	**0.31**		**0.35**				**0.33**
	95% CI		0.19, 0.81	0.30, 1.12	0.27, 1.02		0.08, 1.06	0.08, 1.18	0.11, 1.39		0.12, 0.92	0.12, 0.90	0.13, 0.99		0.18, 0.83	0.33, 1.41		0.14, 1.44	0.05, 0.88		0.19, 1.31	0.1, 0.99		0.09, 1.40				0.06, 1.72
	p value		0.011	0.106	0.056		0.060	0.086	0.148		0.034	0.030	0.047		0.015	0.299		0.177	0.033		0.157	0.048		0.136				0.189
Rate of Exacerbations requiring Hospitalisation	n	155	153	152	156	32	39	29	34	56	54	51	51	191	194	191	45	54	48	64	78	65	**Due to insufficient events no analysis of hospitalisation rate could be performed [for the proposed population] (ITT hospitalisations: 7 in placebo group vs. 0 in mepolizumab group).**					
	Exacerbation rate/year	0.18	0.11	0.12	0.07	0.32	0.16	0.13	0.11	0.39	0.17	0.16	0.10	0.1	0.03	0.06	0.35	0.17	0.07	0.29	0.16	0.08						
Comparison vs placebo	Rate ratio		**0.61**	**0.65**	**0.37**		**0.50**	**0.39**	**0.34**		**0.45**	**0.41**	**0.26**		**0.31**	**0.61**		**0.49**	**0.19**		**0.55**	**0.28**							
	95% CI		0.28, 1.33	0.31, 1.39	0.16, 0.88		0.13, 1.97	0.08, 1.91	0.07, 1.62		0.14, 1.43	0.13, 1.31	0.07, 0.97		0.11, 0.91	0.23, 1.66		0.11, 2.11	0.03, 1.31		0.15, 2.03	0.05, 1.45							
	p value		0.214	0.268	0.025		0.322	0.247	0.176		0.173	0.132	0.045		0.034	0.334		0.338	0.091		0.372	0.129							
SGRQ	n	**SGRQ was not an endpoint in DREAM**												177	184	174	40	53	42	59	75	58	61	65	15	22	45	51
	LS Mean (SE)													37.7 (1.16)	30.7 (1.13)	31.2 (1.16)	42.4 (2.64)	29.5 (2.32)	32.5 (2.59)	41.3 (2.08)	31.3 (1.86)	33.4 (2.12)	44.3 (1.73)	38.5 (1.68)	44.9 (4.76)	39.9 (3.91)	43.8 (2.17)	38.2 (2.03)
	LS Mean Change (SE)													-9.0 (1.16)	-16.0 (1.13)	-15.4 (1.16)	-8.2 (2.64)	-21.1 (2.32)	-18.1 (2.59)	-8.7 (2.08)	-18.7 (1.86)	-16.6 (2.12)	-3.1 (1.73)	-8.8 (1.68)	-6.5 (4.76)	-11.5 (3.91)	-3.5 (2.17)	-9.1 (2.03)
Comparison vs placebo	Difference														**-7**	**-6.4**		**-12.8**	**-9.9**		**-10**	**-7.9**		**-5.8**		**-5.0**		**-5.6**
	95% CI														-10.2, -3.8	-9.7, -3.2		-19.9, -5.8	-17.2, -2.5		-15.5, -4.5	-13.8, -2.0		-10.6, -1.0		-17.7, 7.7		-11.6, 0.4
	p value														<0.001	<0.001		<0.001	0.009		<0.001	0.008		0.019		0.427		0.066
ACQ[1]	n	121	127	126	129	23	32	22	25	43	45	41	41	170	173	161	40	51	41	58	73	57	53	58	13	19	42	45
	LS Mean (SE)	1.72 (0.08	1.56 (0.08	1.45 (0.08	1.52 (0.086)	2.18 (0.246)	1.71 (0.221	1.75 (0.260)	1.57 (0.241)	1.94 (0.176)	1.76 (0.17	1.50 (0.18	1.55 (0.183)	1.7 (0.0	1.26 (0.06	1.28 (0.070	2.06 (0.1	1.1 (0.12	1.34 (0.13	1.97 (0.11	1.18 (0.10	1.43 (0.114)	1.98	1.46 (0.12	2.61 (0.311)	1.73 (0.259)	2.08 (0.15	1.43 (0.143

		7)	7)	6)			)				8)	6)		69)	8	)	39)	5)	6)	3)	2		(0.1 28)	6)			0)	)
	LS Mean Change (SE)	-0.59 (0.08 7)	-0.75 (0.08 7)	-0.87 (0.08 6)	-0.80 (0.086)	-0.33 (0.246)	-0.80 (0.221)	-0.76 (0.260)	-0.94 (0.241)	-0.55 (0.176)	-0.73 (0.17 8)	-0.99 (0.18 6)	-0.95 (0.183)	-0.5 0 (0.0 69)	-0.94 (0.06 8)	-0.92 (0.070)	-0.27 (0.1 39)	-1.23 (0.12 5)	-0.98 (0.13 6)	-0.38 (0.11 3)	-1.17 (0.10 2)	-0.92 (0.114)	-0.0 9 (0.1 28)	-0.61 (0.12 6)	0.22 (0.311)	-0.66 (0.259)	-0.04 (0.15 0)	-0.69 (0.143)
Comparison vs placebo	Difference		**-0.16**	**-0.27**	**-0.2**		**-0.47**	**-0.43**	**-0.61**		**-0.17**	**-0.44**	**-0.39**		**-0.44**	**-0.42**		**-0.96**	**-0.72**		**-0.79**	**-0.54**		**-0.52**		**-0.88**		**-0.65**
	95% CI		-0.39, 0.07	-0.51, -0.04	-0.43, 0.03		-1.09 0.16	-1.10, 0.24	-1.26, 0.04		-0.65, 0.30	-0.92, 0.05	-0.88, 0.09		-0.63, -0.25	-0.61, -0.23		-1.33, -0.59	-1.10, -0.33		-1.09, -0.49	-0.86, -0.23		-0.87, -0.17		-1.71, -0.05		-0.106, -0.24
	p value		0.183	0.02	0.085		0.142	0.206	0.066		0.473	0.076	0.113		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001		0.004		0.038		0.002
OCS Reduction	n																						66	69	15	22	48	54
% OCS reduction during week 20-24	90% - 100% **(%)**																						7(11)	16 (23)	2 (13)	3 (14)	6 (13)	10 (19)
	75% - <90% **(%)**																						5 (8)	12 (17)	1 (7)	5 (23)	5 (10)	9 (17)
	50% - <75% **(%)**																						10 (15)	9 (13)	1 (7)	3 14)	7 (15)	7 (13)
	>0% - <50% **(%)**																						7 (11)	7 (10)	1 (7)	2 (9)	4 (8)	6 (11)
	No change or any increase or lack of asthma control or withdrawal from treatment (%)																						37 (56)	25 (36)	10 (67)	9 (41)	26 (54)	22 (41)
Comparison vs placebo	Odds Ratio to Placebo																							2.39		**2.75**		**1.81**
	95% CI																							1.25, 4.56		**0.72, 10.59**		**0.86, 3.79**
	p-value																							0.008		**0.140**		**0.115**
≥50% Reduction in Daily OCS Dose, n (%)	n																						66	69	15	22	48	54
	50% to 100%																						22 (33)	37 (54)	4 (27)	11 (50)	18 (38)	26 (48)
	<50%, no decrease in OCS, lack of asthma control, or withdrawal from treatment																						44 (67)	32 (46)	11 (73)	11(50)	30 (63)	28 (52)
Comparison vs placebo	Odds ratio to placebo																							2.26		2.93		1.60
	95% CI																							1.10, 4.65		0.68, 12.53		0.70, 3.64
	p-value																							0.027		0.147		0.266
Reduction in Daily OCS Dose to ≤5 mg, n (%)	n																						66	69	15	22	48	54
	Reduction to ≤5 mg																						21 (32)	37 (54)	5 (33)	11 (50)	19 (40)	27 (50)
	Reduction to >5 mg, lack of asthma control, or withdrawal from treatment																						45 (68)	32 (46)	10 (67)	11 (50)	29 (60)	27 (50)
Comparison vs placebo	Odds ratio to placebo																							2.45		2.68		1.64
	95% CI																							1.12, 5.37		0.52, 13.70		0.68, 3.93
	p-value																							0.025		0.237		0.268
Total Reduction of OCS Dose, n (%)	n																						66	69	15	22	48	54
	Total (100%) reduction (0 mg)																						5 (8)	10 (14)	1 (7)	2 (9)	4 (8)	7 (13)

Not an endpoint in DREAM

Not an endpoint in MENSA

	OCS taken, lack of asthma control, or withdrawal from treatment																
														61 (92)	59 (86)	14 (93)	20 (91)	44 (92)	47 (87)
Comparison vs placebo	Odds ratio to placebo														1.67	Due to insufficient events no statistical analysis performed			1.35
	95% CI														0.49, 5.75				0.32, 5.78
	p-value														0.414				0.684
Median Percentage Reduction in Daily OCS Dose	n													66	69	15	22	48	54
	Median (%)													0.0	50.0	0.0	48.1	0.0	36.5
	95% CI of the median													-20.0, 33.3	20.0, 75.0	-270, 66.7	0.0, 80.0	0.0, 50.0	0.0, 66.7
	Median difference														-30.0		33.3		-14.3
Comparison vs placebo	95% CI of the median difference														-66.7, 0.0		-11.1, 90.1		-50, 0.0
	p-value														0.007		0.236		0.162
AQLQ	n	123	128	127	129	23	33	23	25	44	46	44	41	**AQLQ was not an endpoint in MENSA**			**AQLQ was not an endpoint in SIRIUS**		
	LS Mean (SE)	4.92 (0.090)	5.00 (0.089)	4.97 (0.088)	5.14 (0.088)	4.63 (0.209)	5.01 (0.181)	4.81 (0.216)	5.18 (0.201)	4.87 (0.149)	5.03 (0.148)	4.97 (0.155)	5.13 (0.154)						
	LS Mean Change (SE)	0.71 (0.090)	0.80 (0.089)	0.77 (0.088)	0.93 (0.088)	0.47 (0.209)	0.85 (0.181)	0.66 (0.216)	1.02 (0.201)	0.64 (0.149)	0.81 (0.148)	0.75 (0.155)	0.91 (0.154)						
Comparison vs placebo	Difference		0.08	0.05	0.22		0.38	0.19	0.55		0.17	0.11	0.27						
	95% CI		-0.16, 0.32	-0.19, 0.29	-0.02, 0.46		-0.14, 0.90	-0.37, 0.75	0.00, 1.10		-0.23, 0.57	-0.30, 0.51	-0.14, 0.68						
	p value		0.501	0.664	0.069		0.151	0.511	0.049		0.413	0.601	0.199						
EQ-5D	n	127	130	129	132	25	32	24	27	45	46	44	43	**EQ-5D was not an endpoint in MENSA**			**EQ-5D was not an endpoint in SIRIUS**		
Week 52 Index score	Mean (SD)	0.82 (0.214)	0.81 (0.209)	0.83 (0.194)	0.82 (0.212)	0.79 (0.154)	0.81 (0.224)	0.79 (0.198)	0.86 (0.221)	0.78 (0.221)	0.82 (0.202)	0.81 (0.193)	0.85 (0.207)						
	Median	0.85	0.81	0.85	0.85	0.80	0.80	0.80	1.00	0.80	0.80	0.80	1.00						
	Min, Max	-0.2, 1.0	-0.2, 1.0	0.1, 1.0	0.0, 1.0	0.5 1.0	-0.2, 1.0	0.1, 1.0	0.2, 1.0	0.1, 1.0	-0.2, 1.0	0.1, 1.0	0.2, 1.0						
Week 52 Change from Baseline	n	127	130	128	132	25	32	24	27	45	46	44	43						
	Mean (SD)	0.07 (0.221)	0.08 (0.252)	0.11 (0.207)	0.09 (0.195)	-0.05 (0.146)	0.04 (0.302)	0.04 (0.157)	0.13 (0.223)	-0.03 (0.194)	0.05 (0.268)	0.07 (0.177)	0.13 (0.212)						
	Median	0.04	0.03	0.03	0.01	0.00	0.05	0.00	0.07	0.00	0.05	0.00	0.04						
	Min, Max	-0.6, 0.8	-1.0, 1.2	-0.6, 0.6	-0.5, 0.6	-0.3, 0.3	-1.0, 0.6	-0.4, 0.4	-0.5, 0.6	-0.5, 0.4	-1.0, 0.6	-0.4, 0.6	-0.5, 0.6						

1. The initial ACQ model for SIRIUS did not converge as there were more subjects than time-points for analysis. We have therefore only included data from weeks 4, 8, 12, 16, 20, and 24 in this analysis in order to reach convergence.

A10. Section 4.4 pages 53-59 of the company's submission: Missing data due to patient withdrawals were analysed using a Missing at Random assumption for DREAM and MENSA, with two sensitivity analyses performed (Table 13, page 59). Please provide further information on the methods and key findings of these analyses. Please also clarify the findings for the sensitivity analysis performed for missing data in SIRIUS.

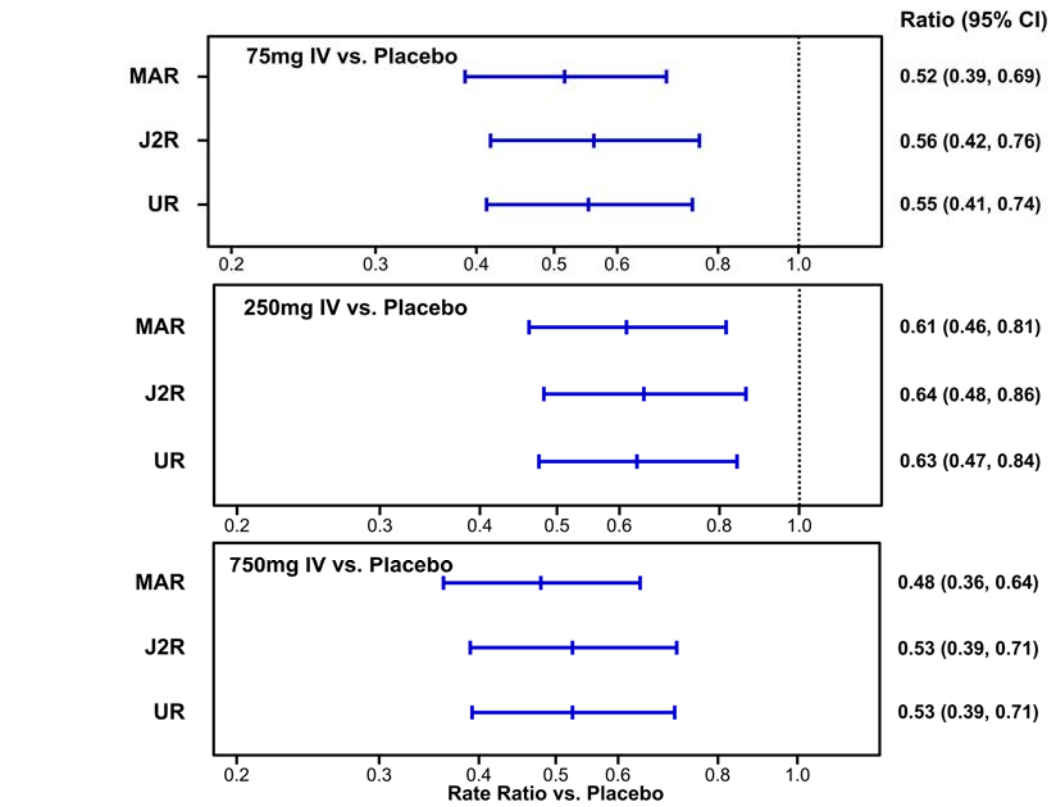
The primary analysis of rate of clinically significant exacerbations in DREAM and MENSA using the negative binomial model assumed that missing data was missing at random (MAR). To examine the sensitivity of the results of the primary analysis to departures from this assumption, two further sensitivity analyses were performed using multiple imputation methods based on pattern mixture models as described in Keene et al (2014). This approach models the missing data for the mepolizumab treatment arm based on the results of the placebo arm.

The assumptions used to impute the missing part of the data for subjects who withdrew early were as follows:

a) Jump to Reference (J2R): Missing counts were imputed conditional upon the subjects own observed number of events prior to withdrawal. The impact of sampling from this conditional distribution was that if their event rate prior to withdrawal was worse than would be expected (positive residual) on mepolizumab, their imputed event rate after withdrawal would be worse than the expected event rate on placebo. Missing data in the placebo arm were imputed under randomized arm MAR.
b) Unconditional Reference (UR): The basis of this approach was that withdrawal from mepolizumab represented a new episode for the subject and the previous history of events was not used in the imputation model for events post-withdrawal. Instead, missing events for mepolizumab were imputed using the overall mean for placebo, conditional only on baseline covariates. Missing data in the placebo arm were again imputed under randomized-arm MAR.

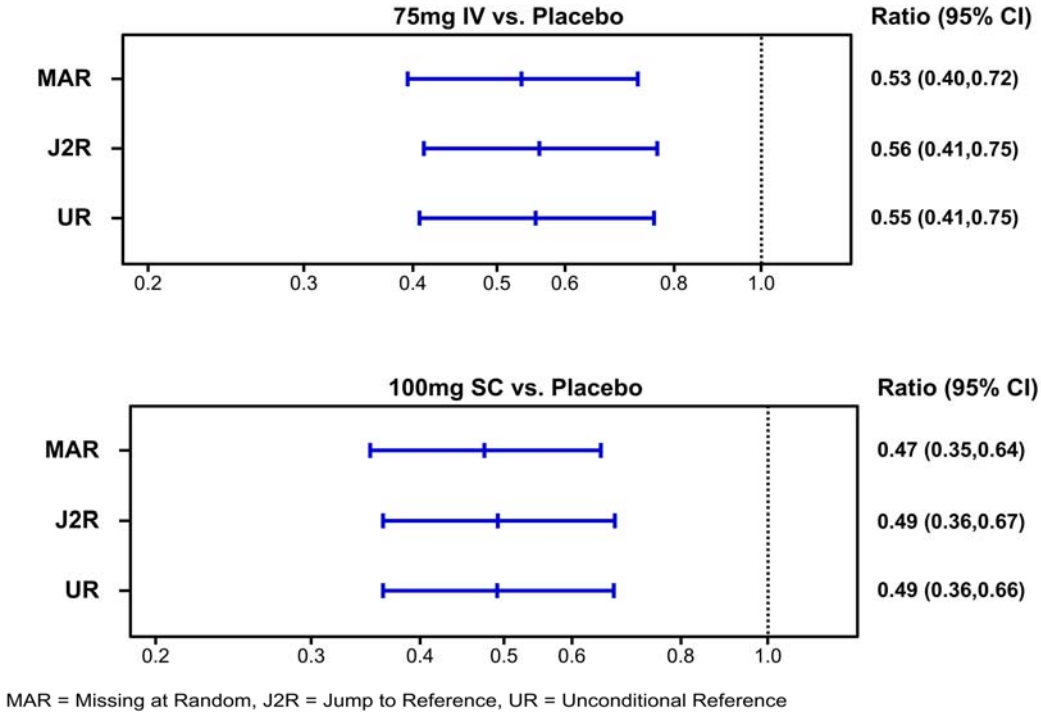
Results of these sensitivity analyses for DREAM and MENSA are shown in Figure 1 and Figure 2 below, together with the results from the primary analysis which assumes MAR.

Figure 1: DREAM - sensitivity analyses for missing data



MAR = Missing at Random, J2R = Jump to Reference, UR = Unconditional Reference

Figure 2: MENSA - sensitivity analyses for missing data



MAR = Missing at Random, J2R = Jump to Reference, UR = Unconditional Reference

In SIRIUS, for the primary analysis of OCS reduction, all subjects in the ITT Population were included. Subjects who withdrew early or who had missing data were assigned to the lowest efficacy category. Sensitivity analysis was performed by assigning subjects to the efficacy category according to the reduction they had obtained by the time of their withdrawal (average dose in the 28 days prior to withdrawal).

Table 3 shows the results of the primary analysis and of the sensitivity analysis.

Table 3: SIRIUS: Analysis of OCS Percent Reduction from Baseline during Weeks 20 24 by Reduction Categories

	Primary Analysis1		Sensitivity Analysis2	
	Number (%) of Subjects		Number (%) of Subjects	
Percent Reduction from Baseline	Placebo N=66	Mepolizumab 100 mg SC N=69	Placebo N=66	Mepolizumab 100 mg SC N=69
N	66	69	66	69
90% to 100%	7 (11)	16 (23)	7 (11)	16 (23)
75% to <90%	5 (8)	12 (17)	5 (8)	12 (17)
50% to <75%	10 (15)	9 (13)	10 (15)	9 (13)
>0% to <50%	7 (11)	7 (10)	8 (12)	8 (12)
No decrease in OCS, lack of asthma control	37 (56)	25 (36)	36 (55)	24 (35)
Odds ratio to placebo	---	2.39	---	2.38
95% CI	---	(1.25, 4.56)	---	(1.25, 4.52)
p-value	---	0.008	---	0.008

1. Primary analysis: withdrawn subjects assigned to worst category
2. Sensitivity analysis: withdrawn subjects assigned to efficacy category applicable prior to withdrawal

Reference:
Keene ON, Roger JH, Hartley BF, Kenward MG. Missing data sensitivity analysis for recurrent event data using controlled imputation. Pharmaceutical Statistics 2014, 13:258–264.

A11. Please clarify whether the difference between study groups in the number of exacerbations that require hospitalisations in the preceding year in MENSA are theoretically likely to impact on the observed results. For information, in the company's proposed population (calculated from Table 17): 13% of the placebo arm had 3 or more exacerbations compared with 2% in the mepolizumab 75mg IV arm and 6% in the mepolizumab 100mg SC arm.

While there are small differences in the baseline hospitalisation rate in the GSK proposed population vs the ITT population, these differences appear not to affect the trend in reduction of rate of exacerbations requiring hospitalisation seen in the GSK proposed population (45% in 100mg SC, table 26, page 86), which was comparable to both the ITT population (69% in 100mg SC, table 36, page 95) and indeed the pooled population of DREAM and MENSA (50% in pooled 75mg IV and 100mg SC, table 55, page 123).

We have shown that baseline exacerbation rate, including hospitalisations is consistently reduced in the ITT population (please see

Table 4). In the ITT population 18% (35/191) of the placebo, 21% (41/191) of the 75mg IV and 17% (33/194) of the 100mg SC arm required hospitalisations at baseline. <6%, 1% and <5% experienced 3 or more hospitalisations, respectively. In the pooled analysis of DREAM and MENSA in the placebo arm 5% (16/346) and 2% (10/538) of the pooled 75mg IV and 100mg SC arm had more than 2 exacerbations at baseline (table 51, page 120).

Table 4: Rate of baseline exacerbations (MENSA, ITT population)

Characteristic		MENSA (N=576)		
		Mepo		Placebo
		75 IV (n=191)	100 SC (n=194)	(n=191)
Exacerbations requiring admission in year prior to study start, n (%)		41 (21)	33 (17)	35(18)
Number of exacerbations that required hospitalisation	3	2 (1%)	5 (3%)	5 (3%)
	4	0	1 (<1%)	1 (<1%)
	>4	0	1 (<1%)	4 (2%)

The number of patients requiring hospitalisations in the individual ITT trials was small and thus even smaller in the GSK proposed population. Indeed, the number of patients that had 3 or more exacerbations requiring hospitalisation in the MENSA proposed population was 7 out of 45 patients in the placebo, 1 out of 48 in 75mg IV arm and 5 out of 54 in the 100mg SC arm. The total number of patients requiring any number of hospitalisations at baseline was 18, 16 and 15 in each arm respectively. The small number of patients with 3 or more exacerbations requiring hospitalisation lacked statistical power and made the data more difficult to interpret.

In conclusion, the number of patients requiring hospitalisation due to an exacerbation was small in all mepolizumab trials. Indeed the number of patients with 3 or more hospitalisations was even smaller. However, the consistent trends in exacerbation reduction, including those leading to hospitalisation suggest that mepolizumab's effect on exacerbation rate is robust and consistent. Therefore, it is unlikely that the difference between study groups in the number of exacerbation that require hospitalisations in the preceding year in MENSA would have an impact on the observed results.

(Please also see answer to question A13 for SIRIUS data.)

A12. Page 167 of the company's submission: Please provide additional details about the systemic reactions and hypersensitivity reactions, including the comparative data between placebo and mepolizumab arms, the seriousness of the events, and any sequelae. Please provide tables detailing the "adverse events of special interest" for the key efficacy trials and for the open label extension trials.

<u>Placebo Controlled Severe Asthma Studies (PCSAs)</u>

Further information regarding the adverse events of special interest can be found in the respective CSRs (DREAM, Table 44 and 45 page 106 [also refer to page 1453]; MENSA, Table 48 page 114 [also refer to page 724]; SIRIUS, Table 42 page 90).

Across all three trials and in both placebo and mepolizumab arms, infections were the most common adverse event of special interest, followed by systemic/local site reactions. The tables below show, when comparing placebo with the mepolizumab arms, the number of infections occurring were similar. There were some differences in the occurrence of systemic/local site reactions with the mepolizumab SC arm showing increased incidence compared to placebo.

<u>DREAM</u>

A summary of AEs or SAEs in DREAM, defined by the Investigator as an infusion-related reaction, hypersensitivity reaction or local injection site reactions and assessed as possibly related to investigational product is presented in Table 5, along with other AEs of special interest.

Table 5: Adverse Events defined by the Investigator as an Infusion-Related Reaction, Hypersensitivity or Local Injection Site Reaction and Assessed as Possibly Related to Investigational Product (DREAM, ITT Population)

SAE/AEs of special interest	Number (%) of Subjects		Relative Risk (95% CI)	% Risk Difference (95% CI)
	Placebo n=155	Mepolizumab All doses IV n=461		
All SAEs	25 (16.1)	63 (13.7)	0.85 (0.55, 1.30)	-2.5% (-11.6, 6.6)
Any Infusion-Related Reaction Event	13 (8.4)	43 (9.3)[1]	1.11 (0.61, 2.01)	0.9% (-8.2, 10.1)
Infusion-related reaction	10 (6)	39		
Hypersensitivity	3 (2)	3		
Type IV hypersensitivity reaction	0	2		
Any Local injection site reaction event	5 (3)	5 (3)		
All Infections	89 (57.4)	265 (57.5)	1.00 (0.86, 1.17)	0.1% (-9.0, 9.2)
Serious	5 (3.2)	15 (3.3)	1.01 (0.37, 2.73)	0.0% (-9.0, 9.2)
Neoplasms	1 (0.6%)	3 (0.7)	1.01 (0.11, 9.63)	0.0% (-9.1, 9.1)
Malignancies	0	2 (0.4)		0.4% (-8.7, 9.5)
Cardiac Events	4 (2.6%)	16 (3.5)	1.34 (0.46, 3.96)	0.9% (-8.2, 10.0)
Serious	1 (0.6%)	7 (1.5)	2.35 (0.29, 19.0)	0.9% (-8.2, 10.0)
Serious CVT events	3 (1.9%)	10 (2.2)	1.12 (0.31, 4.02)	0.2% (-8.8, 9.4)
Serious ischaemic events	2 (1.3%)	5 (1.1)	0.84 (0.16, 4.29)	-0.2% (-9.3, 8.9)

1. Some patients may have more than one Infusion-Related Reaction Event, patients are counted against each individual type of event but only once in the overall total Infusion-Related Reaction Events. Thus, the total Infusion-Related Reaction Event number may vary from the sum of all types of Infusion-Related Reaction Events.

The relative risk and risk difference for adverse events of special interest was examined for placebo and mepolizumab (all doses combined). Infections were the most frequently reported AE of special interest and occurred with a similar incidence between treatments: 57.4% placebo and 57.5% mepolizumab. Infusion-related reactions were the next most frequent and also occurred with a similar incidence between treatments: 8.4% placebo, 9.3% mepolizumab. Relative risk was at or near 1 for both of these AEs. Cardiac events and neoplasms were reported in a small proportion of subjects (≤3.5% and <1%, respectively) and the confidence intervals for the relative risk between treatments were wide.

The investigators also recorded symptoms associated with all local site reactions, which have been summarised in Table 6 (for all symptoms that occurred in ≥2 subjects in any treatment group).

Table 6: Summary of Symptoms Associated with Infusion-Related Reactions Reported in more than or equal to 2 subjects in any treatment group (DREAM, ITT Population)

	Placebo n=55 n (%)	Mepolizumab 75mg n=153 n (%)	Mepolizumab 250mg n=152 n (%)	Mepolizumab 750mg n=156 n (%)
Number of subjects reporting an infusion-related reaction	13 (8)	8 (5)	15 (10)	20 (13)
Headache	4	4	5	6
Dizziness	2	2	1	6
Nausea	3	2	3	2
Fatigue	1	0	4	3
Pruritis	1	0	3	4
Urticaria	1	0	3	2
Asthenia	1	2	0	1
Myalgia	0	1	1	2
Rash	1	0	1	2
Vomiting	3	0	0	1
Arthralgia	0	0	1	2

MENSA

In MENSA, the relative risk and risk difference for adverse events of special interest was examined for placebo and mepolizumab. Of these events, infections were reported most frequently and occurred with a slightly lower incidence in the mepolizumab 100 mg SC group (53%) compared with the mepolizumab 75 mg IV group (62%) and placebo group (59%); the relative risk for these events compared to placebo was 0.89 for mepolizumab 100 mg SC and 1.04 for mepolizumab 75 mg IV. Serious infections occurred at the same frequency of 3% in the placebo and mepolizumab 100 mg SC groups and 1% in the mepolizumab 75 mg IV group.

Systemic and local site reactions occurred with a higher incidence in the mepolizumab 100 mg SC group (10%) compared with the mepolizumab 75 mg IV group (5%) and the placebo group (6%); for the mepolizumab 100 mg SC group the relative risk was greatest for local site reactions (2.39). Cardiac disorders, opportunistic infections, and malignancies were reported by 5 or fewer subjects in each treatment group. This has been summarised in Table 7.

Table 7: Summary of Serious AEs and AEs of Special Interest: Incidence , Relative Risk and Risk Difference: Mepolizumab 75 mg IV and 100 mg SC (On-treatment) (MENSA, ITT Population)

SAE/AEs of special interest	Number (%) of Subjects			Mepolizumab 75mg IV n = 191		Mepolizumab 75mg IV n = 194	
	Placebo n=191	Mepolizumab 75mg IV n=191	Mepolizumab 100mg SC n=194	Relative Risk (95% CI)	% Risk Difference (95% CI)	Relative Risk (95% CI)	% Risk Difference (95% CI)
SAEs	27 (14)	14 (7)	16 (8)	0.52 (0.28, 0.96)	-6.8% (-17.0, 3.5)	0.58 (0.32, 1.05)	-5.9% (-15.8, 4.3)
Systemic/Local Reactions	11 (6)	10 (5)	19 (10)[3]	0.91 (0.40, 2.09)	-0.5% (-10.8, 9.7)	1.70 (0.83, 3.48)	4.0% (-5.9, 14.1)
Systemic (hypersensitivity)	4 (2)	4 (2)	3 (2)	1.00 (0.25, 3.94)	0.0% (-10.3, 10.3)	0.74 (0.17, 3.26)	-0.5% (-10.5, 9.5)
Local Site	7 (4)	6 (3)	17 (9)	0.86 (0.29, 2.50)	-0.5% (-10.8, 9.7)	2.39 (1.01, 5.63)	5.1% (-4.8%, 15.1)
Anaphylaxis	0	0	0				
All Infections	113 (59)	118 (62)	102 (53)	1.04 (0.89, 1.23)	2.6% (-7.7, 12.9)	0.89 (0.74, 1.06)	-6.6% (-16.6, 3.4)
Serious	5 (3)	1 (1)	6 (3)	0.20 (0.02, 1.70)	-2.1% (-12.3, 8.2)	1.18 (0.37, 3.81)	0.5% (-9.5, 10.5)
Opportunistic	0	1 (1)	3 (2)		0.5% (-9.7, 10.8)		1.5% (-8.4, 11.5)
Neoplasms	5 (3)	2 (1)	2 (1)	0.40 (0.08, 2.04)	-1.6% (-11.8, 8.7)	0.39 (0.08, 2.01)	-1.6% (-11.5, 8.4)
Malignancies	0	0	0				
Cardiac Disorders	5 (3)	4 (2)	4 (2)	0.80 (0.22, 2.93)	-0.5% (-10.8, 9.7)	0.79 (0.21, 2.89)	-0.6% (-10.5, 9.5)
Serious	0	0	1 (1)				0.5% (-9.5, 10.5)
Serious CVT events	0	0	1 (1)				0.5% (-9.5, 10.5)
Serious ischaemic events	0	0	0				

1. Malignancies obtained via the Neoplasms benign, malignant and unspecified (including cysts and polyps) System Organ Class. Infections obtained via the Infections and infestations System Organ Class. Cardiac disorders obtained via the Cardiac disorders System Organ Class.
2. Identified by the Safety Review Team 3. Some patients may have more than one Infusion-Related Reaction Event, patients are counted against each individual type of event but only once in the overall total Infusion-Related Reaction Events. Thus, the total Infusion-Related Reaction Event number may vary from the sum of all types of Infusion-Related Reaction Events.

Note: CVT = cardiac, vascular, and thromboembolic

Subjects in the placebo group reported associated symptoms of bronchospasm and dizziness in addition to some of the same symptoms reported by the mepolizumab groups (fatigue, pruritus and rash). A summary of the associated symptoms have been shown in Table 8.

Table 8: Summary of Symptoms Associated with AEs Defined by the Investigator as being Systemic Infusion/Injection Reactions (MENSA, ITT Population)

	Placebo n=191	Mepolizumab	Mepolizumab

		75mg IV n=191	100mg SC n=194
All systemic infusion/injection related reactions Number of subjects	4 (2%)	4 (2%)	3 (2%)
Bronchospasm	1	0	0
Dizziness	1	0	0
Fatigue	1	0	1
Other	2	3	3
Pruritus	1	1	0
Rash	1	1	1
Urticaria	0	1	0

All systemic reactions were reported as either mild or moderate in intensity and all resolved/recovered except for one unresolved Type IV hypersensitivity reaction reported by a subject in the mepolizumab 75 mg IV group. This event occurred after the last dose was administered in MENSA and the subject went on to enrol in OLE COSMOS without reports of similar reactions following subsequent doses of mepolizumab in COSMOS.

SIRIUS

In SIRIUS, the relative risk and risk difference for these events was examined for mepolizumab compared with placebo. Of these events, infections were reported most frequently and occurred with a higher incidence in the placebo group (56%) compared with the mepolizumab group (49%); the relative risk was 0.88. Systemic and local site reactions were the next most frequent and occurred with a slightly higher incidence in the mepolizumab group (10%) compared with the placebo group (6%); the relative risk was 1.28 for systemic reactions and 1.91 for local site reactions. Cardiac disorders, serious and opportunistic infections, and malignancies were reported in a small number of subjects in each treatment group (n=0 to 4). This has been summarised in Table 9.

Table 9: Serious AEs and AEs of Special Interest: Incidence, Relative Risk and Risk Difference (SIRIUS, ITT Population)

SAE/AEs of special interest	Number (%) of Subjects		Relative Risk (95% CI)	% Risk Difference (95% CI)
	Placebo n=66	Mepolizumab 100mg SC n=69		
All SAEs	12 (18)	1 (1)	0.08 (0.01, 0.60)	-16.7 (-33.0, 0.5)
Systemic/Local Reactions	4 (6)	7 (10)[1]	1.67 (0.51, 5.45)	4.1 (-12.7, 21.1)
Systemic	3 (5)	4 (6)	1.28 (0.30, 5.48)	1.3 (-15.4, 18.3)
Local Site	2 (3)	4 (6)	1.91 (0.36, 10.10)	2.8 (-14.0, 19.7)
Anaphylaxis	0	0		
All Infections	37 (56)	34 (49)	0.88 (0.64, 1.21)	-6.8 (-23.7, 10.3)
Serious	4 (6)	1 (1)	0.24 (0.03, 2.08)	-4.6 (-21.2, 12.5)
Opportunistic	1 (2)	0		-1.5 (-18.3, 15.4)
Malignancies	3 (5)	0		-4.5 (-21.2, 12.5)
All Cardiac Disorders	3 (5)	2 (3)	0.64 (0.11, 3.70)	-1.6 (-18.3, 15.4)
Serious	0	0		
Serious CVT events	0	0		
Serious ischaemic events	0	0		

1. Some patients may have more than one Infusion-Related Reaction Event, patients are counted against each individual type of event but only once in the overall total Infusion-Related Reaction Events. Thus, the total Infusion-Related Reaction Event number may vary from the sum of all types of Infusion-Related Reaction Events. Note: CVT = cardiac, vascular, and thromboembolic

The symptoms associated with these systemic reactions were different in the placebo group (dizziness, fatigue, headache, and hypotension) compared with the mepolizumab group (myalgia, rash, chills, fasciculations in both hands, flushing in the head, flash, and mouth tingling). These are shown in Table 10.

Table 10: Systemic infusion/injection related reactions in placebo group vs. mepolizumab group (SIRIUS, ITT Population)

	Placebo n=66	Mepolizumab 100mg SC n=69
All systemic infusion/injection related reactions Number of subjects	3 (5%)	4 (6%)
Dizziness	2	0
Fatigue	2	0
Headache	1	0
Hypotension	1	0
Myalgia	0	2
Rash	0	2
Other: chills during 15 mins, in 48 hours after injection	0	1
Other: fasciculations both hands after injection	0	1
Other: flash	0	1
Other: flushing in the head	0	1
Other: flushing in the head and red face	0	1
Other: mouth tingling	0	1

Open Label Extension Studies

COLUMBA

Systemic Reactions

No subjects reported anaphylaxis. Six subjects experienced investigator-defined systemic reactions, which included hypersensitivity, injection-related reaction, rash, and Type IV hypersensitivity reaction (please see Table 11).

Table 11: Summary of AEs defined by the Investigator as being Systemic Infusion/Injection Site Reactions (COLUMBA, ITT Population)

Preferred Term	Mepolizumab 100mg SC n=347
ANY EVENT	6 (2%)
Hypersensitivity	2 (<1%)
Injected related reaction	2 (<1%)
Rash	1 (<1%)
Type IV hypersensitivity reaction	1 (<1%)

The symptoms associated with these systemic reactions included headache, pruritus, rash, urticaria, and “other” (symptom not defined) as shown in the Table 12. None of these 6 subjects experienced systemic reactions during the DREAM study.

Table 12: Summary of Symptoms Associated with AEs Defined by the Investigator as being Systemic Infusion/Injection Site Reactions (COLUMBA, ITT Population)

	Mepolizumab 100mg SC n=347
All systemic infusion/injection related reactions Number of subjects	6 (2%)
Headache	2

Other	1
Pruritis	1
Rash	1
Urticaria	1

Other Adverse Events of Special Interest

AEs of special interest also included: local site reactions, cardiac events, serious infections and infestations, and malignancies. These have been summarised in Table 13.

Table 13: Summary of other Adverse Events of Special Interest (COLUMBA, ITT Population)

	Number of Subjects (%) Mepolizumab 100mg SC n =347
Local Injection Site Reactions	31 (9%)
Infections and Infestations	214 (62%)
Serious	4 (1%)
Opportunistic	1 (<1%)
Neoplasms	5 (1%)
Malignancies (SAEs)	2 (<1%)
Cardiovascular Events	13 (4%)
Arrhythmias	8 (2%)
Myocardial Infarction/unstable angina	3 (<1%)
Cerebrovascular events stroke and TIA	1 (<1%)
Revascularisation	1 (<1%)
All cause deaths	1 (<1%)

COSMOS

Systemic reactions

Thirteen subjects (2%) experienced investigator-defined systemic reactions, which included injection related/non-allergic reaction (7 subjects; 1%), hypersensitivity/allergic (4 subjects, <1%), and delayed reactions recorded as Type IV hypersensitivity reaction (3 subjects, <1%). This is summarised in Table 14.

Table 14: Summary of AEs defined by the investigator as being Systemic reactions (COSMOS, ITT Population)

Preferred Term	**Mepolizumab 100mg SC n=651**
ANY SYSTEMIC REACTION	13 (2%)
Injected related/non-allergic reaction	7 (1%)
Hypersensitivity/allergic	4 (<1%)
Type IV hypersensitivity reaction	3 (<1%)

The symptoms associated with these systemic reactions included rash (3 subjects), pruritus (3 subjects), and headache (2 subjects). Diarrhoea, ascending heat, pain on both underarms, sore throat, red eyes, sneezing, swollen eyes, facial hot flashes, dyspnoea, angioedema, arthralgia bronchospasm, myalgia, and diffuse erythema were reported in one subject each. This has been summarised in Table 15.

Table 15: Summary of Symptoms Associated with AEs Defined by the Investigator as being Systemic Reactions (COSMOS, ITT Population)

Preferred Term	Mepolizumab 100mg SC n=651
Rash	3 (<1%)
Pruritus	3 (<1%)
Headache	2 (<1%)
Diarrhoea	1 (<1%)
Ascending heat	1 (<1%)
Pain on both underarms	1 (<1%)
Sore throat	1 (<1%)
Red eyes	1 (<1%)
Sneezing	1 (<1%)
Swollen eyes	1 (<1%)
Facial hot flashes	1 (<1%)
Dyspnoea	1 (<1%)
Angioedema	1 (<1%)
Arthalgia	1 (<1%)
Bronchospasm	1 (<1%)
Myalgia	1 (<1%)
Diffuse erythema	1 (<1%)

Of the 13 subjects who experienced investigator-defined systemic reactions during COSMOS, 9 had previously participated in the MENSA study (of those, 6 received placebo and 3 received mepolizumab 100 mg SC). None of these subjects experienced systemic reactions during the MENSA study. Four of the 13 subjects had previously participated in the SIRIUS study and previously received mepolizumab 100 mg SC for 3 subjects and placebo for 1 subject.

Other Adverse Events of Special Interest

AEs of special interest also included: local site reactions, cardiac events, serious infections and infestations, and malignancies. These have been summarised in Table 16.

Table 16: Summary of other Adverse Events of Special Interest (COLUMBA, ITT Population)

	Number of Subjects (%)
	Mepolizumab 100mg SC n =651
Local Injection Site Reactions	29 (4%)
Serious	0 (0%)
Infections and Infestations	455 (70%)
Serious	26 (4%)
Opportunisitc	10 (2%)
Neoplasms	15 (2%)
Serious	5 (<1%)
Cardiovascular Events	15 (2%)
Arrhythmias	6 (<1%)
Congestive Heart Failure	4 (<1%)
Deep vein thrombosis/Pulmonary embolism	2 (<1%)
Cerebrovascular events, Stroke and TIA	1 (<1%)
Myocardial Infarction/Unstable angina	1 (<1%)
Pulmonary hypertension	1 (<1%)

Revascularisation	1 (<1%)
Valvulopathy	1 (<1%)

A13. Please provide the rate of hospitalisations results alone for SIRIUS in the company's proposed population and ITT population.

Please see page 91 for proposed population, it states: 'Due to insufficient events no analysis of hospitalisation rate could be performed (ITT hospitalisations: 7 in placebo group vs. 0 in mepolizumab group).' As there were no exacerbations in the mepolizumab group, the rate of exacerbations requiring hospitalisation is 0. The rate of exacerbations requiring hospitalisation per year for the placebo arm can be calculated by excluding the mepolizumab arm from the analysis, 0.16 per year.

	Placebo	Mepo
Exacerbation rate/year for exacerbations requiring hospitalisation	0.16	0

A14. Section 4.7.3.1 Figure 7, page 77 of the company's submission: The submission illustrates the threshold of eosinophil blood count that predicts a 30% reduction in the rate of exacerbation using a modelling concept. Please provide details of the models used to produce Figure 7.

Modelling analyses were performed in order to predict which patients derive the greatest benefit from treatment with mepolizumab. These analyses firstly identified baseline clinical characteristics that would predict higher or lower rates of exacerbations regardless of treatment and then identified whether any variable was associated with higher or lower reductions in rate with mepolizumab compared to placebo.

Separate analyses were performed of the MENSA and DREAM studies. For both studies, modelling analyses investigated the influence of the following baseline variables in addition to treatment (binary variable: mepolizumab or placebo):

- age (continuous)
- sex (categorical: male, female)
- weight at baseline(continuous)
- region (study MENSA: US, EU, Canada, Japan, Korea, South and Central America, Rest of the World; study DREAM: US, EU, Europe non-EU, South America, Rest of the World)
- number of exacerbations in the year prior to baseline (categorised as 2, 3, or ≥4)
- baseline maintenance use of oral corticosteroids (categorical: yes, no)
- baseline percent predicted pre-bronchodilator FEV1 (continuous: 0%–100%)
- FEV1 reversibility at baseline (categorical: yes, no)
- baseline blood eosinophil count (continuous, logged for analysis)
- baseline IgE concentration (continuous, logged for analysis)

The approach known as 'backwards stepwise selection' was used to identify baseline variables that would predict higher or lower rates of exacerbations regardless of treatment. This involves the following steps:

1. All variables (covariates) are included in the model.
2. The least significant variable above a threshold value (p=0.05 in this case) is removed from the model.

3. Any previously removed variables are re-tested in the model, one-by-one, the most significant variable (if any) below a threshold value (p=0.05) are re-admitted to the model.
4. Repeat until all variables remaining in the model are significant below the threshold value (p=0.05).

Variables that consistently predicted higher or lower rates of exacerbations in addition to treatment for study MENSA were the following:

- number of exacerbations in the year prior to baseline
- baseline maintenance use of OCS
- baseline blood eosinophils

Following the selection of the main effects model, interactions of all covariates with treatment were investigated. This was achieved, for each covariate, by adding to the main-effects model an interaction term between the covariate and treatment and a main effects term for the covariate if not already included in the model. At the 5% significance level, only the interaction term for baseline blood eosinophils was statistically significant ($p<0.05$) for study MENSA.

The final model with main-effects obtained by backwards stepwise selection and interaction terms with treatment statistically significant at $\alpha = 5\%$ included treatment, exacerbations in the year prior to screening, baseline maintenance use of OCS, baseline blood eosinophils, and the interaction between baseline blood eosinophils and treatment. Region was also included as a covariate in the model.

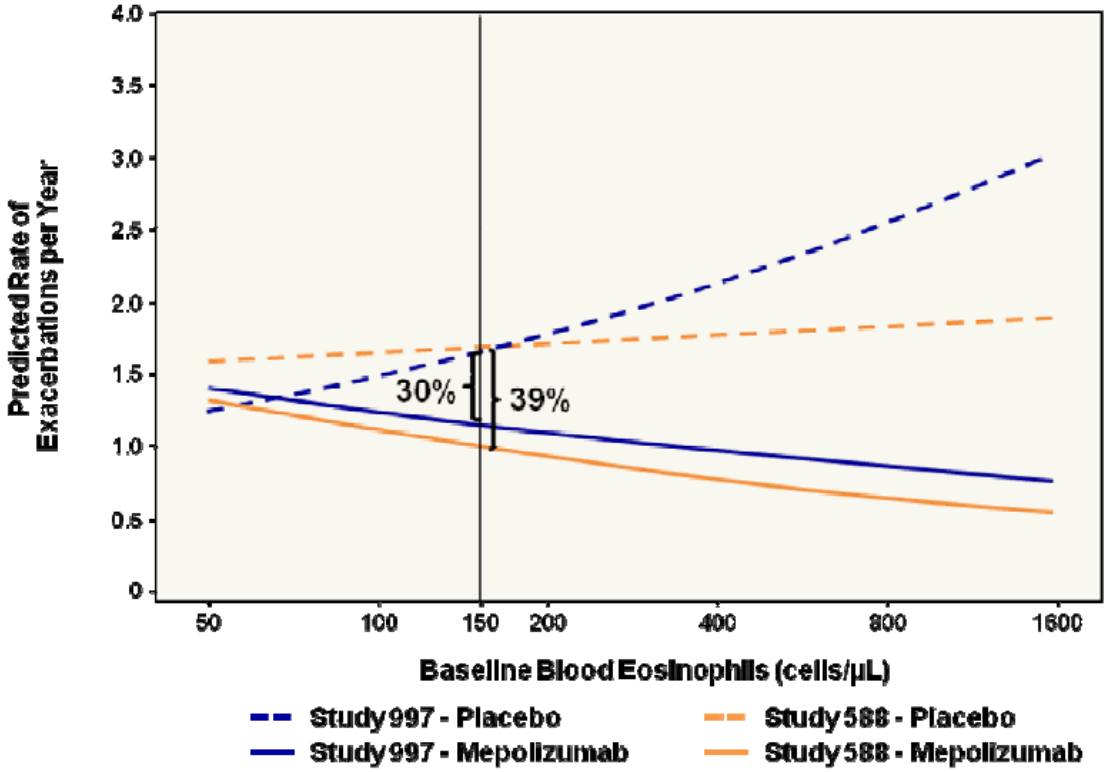
A15. Page 107 of the company's submission: It is stated that in DREAM the "interaction between the number of previous exacerbations and treatment group was potentially significant (p=0.014)". Please provide details of the threshold of eosinophil blood count that predicts a 30% reduction in the rate of exacerbation, separately conditional upon the number of previous exacerbations.

Exacerbations in previous year	Eosinophil level that predicts a 30% reduction	
	Study DREAM	Study MENSA
2 exacerbations	Between 350 and 400 cells/ µL	Between 100 and 150 cells/ µL
3 exacerbations	Between 100 and 150 cells/ µL	Between 50 and 100 cells/ µL
≥4 exacerbations	<50 cells/µL	Between 50 and 100 cells/ µL

The model used to calculate the threshold of eosinophils that predicts a 30% reduction by exacerbations in previous year was the same as used for Figure 7 in the main submission (please also see below) with an additional interaction term for treatment by exacerbations in previous year. While Figure 7 predicts the eosinophil blood count that results in a 30% reduction in exacerbations for patients with ≥2 exacerbations in the previous year, the table above illustrates the blood eosinophil count required to achieve a 30% reduction at a specific baseline exacerbation rate (e.g. only those patients with 2 or 3 exacerbations, excluding those with more than 2 or 3 exacerbations in the previous year). In addition, the DREAM study included patients based on 1 out of 4 inclusion criteria (blood eosinophil count, sputum eosinophil count, FeNO, or deterioration following maintenance medication reduction; please see page 41 & 42 of main submission for full details), while MENSA subjects were specifically selected based on their blood eosinophil count

(≥150cells/μL at initiation of treatment or ≥300 cells/μL in the last 12 months). Thus the MENSA population is more representative of patients that benefit from add-on mepolizumab therapy, which is reflected in the eosinophil data shown in the table above.

Figure 3 (in main submission) Modelling Analysis: Predicted Rate of Exacerbations by Baseline Blood Eosinophil Count (ITT results of DREAM and MENSA)



A16. Section 4.7.3.1 Figure 8 and Table 22, page 79 of the company's submission. Please clarify details of the modelling procedure. Specifically, do the results in Figure 8 reflect those that are presented in Table 22, including correction for the same covariates?

Results from Section 4.7.3.1 Figure 8 and Table 22, page 79 are from two different models.

Table 22 uses the covariates from the pre-specified primary analysis model in MENSA. For this subgroup analysis by previous exacerbation history, covariates fitted were treatment, baseline maintenance OCS use, region and baseline percent predicted FEV1.

Figure 8, presents the results of a model used in DREAM to investigate which patients derive the greatest benefit from treatment from mepolizumab. This model uses covariates of treatment, region, sex, baseline maintenance OCS use, exacerbations in previous year (as an ordinal variable), logarithm of baseline blood eosinophils and an interaction between treatment and exacerbations in previous year.

Study design

A17. Priority Question. (A) Regarding the MENSA and SIRIUS trials, please clarify what led to patients withdrawing during the run-in periods. (B) Please also clarify what the continuation criteria were in MENSA (page 62 – 63 of the company's submission) and SIRIUS (Page 46 and page 65 of the company's submission). (C) Please provide the baseline characteristics of the patients who met the initial eligibility criteria but were not enrolled in the trial (that is, those lost during the run-in phase), preferably in tables alongside patients who were enrolled. (D) Please comment on how this might impact on the generalisability of the MENSA and SIRIUS trial efficacy estimates to clinical practice?

To ensure we answer all aspects of the above question, we have split our answer into parts A to D below.

(A) Table 17 below shows all the reasons for run-in failures and the number of patients associated with each reason within the MENSA study.

Table 17: Summary of Reasons for Run-in Failure (MENSA)

Reason for failure	Total (N= 140)
n	140 (100%)
Adverse event	1 (<1%)
Did not meet continuation criteria	2 (1%)
Did not meet continuation criteria: airway inflammation characterized as eosinophilic in nature as indicated by various criteria	68 (49%)
Did not meet continuation criteria: compliance with completion of e-diary defined by various criteria	19 (14%)
Did not meet continuation criteria: evidence of asthma as documented by various criteria	10 (7%)
Did not meet continuation criteria: liver function test obtained at visit 1 meet various criteria	3 (2%)
Did not meet continuation criteria: no changes in the dose or regimen of baseline ICS and/or additional controller medication (except for treatment of an exacerbation) during the run-in period	2 (1%)
Did not meet continuation criteria: no diagnosis of chronic hepatitis B, as evidenced by positive hepatitis B surface antigen (HBSAG) at visit 1	6 (4%)
Did not meet continuation criteria: no evidence of clinically significant abnormality in the haematological, biochemical or urinalysis screen at visit 1, as judged by the investigator	1 (<1%)
Did not meet continuation criteria: no evidence of significant abnormality in the 12-lead ECG over-read at visit 1	11 (8%)
Did not meet continuation criteria: subjects with an ongoing asthma exacerbation should have their randomisation visit delayed until the investigator considers the subject has returned to their baseline asthma status	5 (4%)
Physician decision: patient on prohibited medication (Lucentis), which falls under exclusion criteria (12)	1(<1%)
Physician decision: technical problem with e-diary	1 (<1%)
Physician decision: the subject didn't met inclusion criteria	1 (<1%)
Physician decision: the subject didn't meet the exclusion criteria	1 (<%)
Physician decision: under investigation for recent cardiac chest pain	1 (<1%)
Protocol violation: protocol deviation	1(<1%)
Withdrawal by subject: 21/12/2012	1 (<1%)
Withdrawal by subject: 31/01/13 Patient called informing that she did not want to participate in trial	1 (<1%)
Withdrawal by subject: because use of log pat is difficult	1 (<1%)
Withdrawal by subject: as the patient's family opposed	1 (<1%)
Withdrawal by subject: for private reasons	1 (<1%)
Withdrawal by subject: patient decided to withdraw his consent	1 (<1%)
Withdrawal by subject: patient had to withdraw due to unexpected out of town family commitment	1 (<1%)
Withdrawal by subject: patient has refused infusions	1 (<1%)
Withdrawal by subject: patient withdrew consent due to personal reasons	1 (<1%)
Withdrawal by subject: patient refused to participate in study	1 (<1%)
Withdrawal by subject: patient wants to get pregnant	1 (<1%)
Withdrawal by subject: patient withdrew consent	1 (<1%)
Withdrawal by subject: patient withdrew consent because her company did not allow site visits as specified by protocol	1 (<1%)

Table 18 below shows all the reasons for run-in failure in the SIRIUS study.

Table 18: Summary of Reasons for Run-in Failure (SIRIUS)

Reason for failure	Total (N= 47)
n	47 (100%)
Did not meet continuation criteria	2 (4%)
Did not meet continuation criteria: asthma : evidence of asthma as indicated in the protocol	2 (4%)
Did not meet continuation criteria: ECG over-read : no evidence of significant abnormality in the 12-lead ECG over-read at Visit 1	3 (6%)
Did not meet continuation criteria: e-diary compliance: compliance with completion of the e-diary as indicated in the protocol	5 (11%)
Did not meet continuation criteria: eosinophilic phenotype: airway inflammation characterised as eosinophilic in nature as indicated in the protocol	10 (21%)
Did not meet continuation criteria: FEV1: persistent airway obstruction as indicated in the protocol	3 (6%)
Did not meet continuation criteria: laboratory abnormality: no evidence of clinically significant abnormality in the haematological, biochemical or urinalysis screen at Visit 1, as judged by the investigator	1 (2%)
Did not meet continuation criteria: liver function: liver function test results obtained at Visit 1 that meet criteria as indicated in the protocol	1 (2%)
Did not meet continuation criteria: optimised OCS dose: achieved a stable dose of OCS during the optimisation period	17 (36%)
Withdrawal by subject: did not want to come back	1 (2%)
Withdrawal by subject: due to private reasons	1 (2%)
Withdrawal by subject: patient called on 1st March 2013 withdrew consent, he felt he was too busy to meet needs of study	1 (2%)
Withdrawal by subject: subject withdrew consent	1 (2%)
Withdrawal by subject: time commitment	1 (2%)

(B) As referenced in the main submission, the continuation criteria including inclusion and exclusion criteria, randomisation criteria and withdrawal criteria for MENSA can be found in the CSR section 4.4 and the MENSA protocol; for SIRIUS they can be found in the CSR section 4.4 and the SIRIUS protocol (please note protocol amendment 1).

(C) In reference to your question regarding run-in failure baseline characteristics, Table 19 below has been created which shows the baseline characteristics of those patients who met the initial eligibility criteria but were not enrolled in the trials (run-in failures) in both MENSA and SIRIUS. These run-in failure baseline characteristics have been entered into the table alongside the ITT populations for both of these studies so comparisons can be made.

Table 19: Table showing Baseline Characteristics for patients lost during the run-in phase as well as the ITT Population (MENSA and SIRIUS)

Characteristic		MENSA		SIRIUS	
		Run-in Failures	ITT	Run-in Failures	ITT
Age (yrs)	n	140	576	47	135
	Mean	53	50.1	54.3	49.9
	SD	14.68	14.28	11.92	12.34
	Median	54	52	57	51

	Min.	12	12	19	16
	Max.	82	82	76	74
	12-17 Years	3 (2%)	25 (4%)	0	2 (1%)
	18-29 Years	7 (5%)	25 (4%)	2 (4%)	6 (4%)
	30-49 Years	39 (28%)	205 (36%)	11 (23%)	45 (33%)
	50-64 Years	60 (43%)	241 (42%)	24 (51%)	68 (50%)
	≥65 Years	31 (22%)	80 (14%)	10 (21%)	14 (10%)
Sex	**n**	140	576	47	135
	Female	96 (69%)	329 (57%)	24 (51%)	74 (55%)
	Male	44 (31%)	247 (43%)	23 (49%)	61 (45%)
Ethnicity	**n**	140	576	47	135
	Hispanic or Latino	7 (5%)	51 (9%)	0	5 (4%)
	Not Hispanic or Latino	133 (95%)	525 (91%)	47 (100%)	130 (96%)
Weight (kg)	**n**	137	576	44	135
	Mean	78.54	76.25	86.93	83.32
	SD	18.454	18.143	23.788	19.796
	Median	77.3	75	82.55	80
	Min.	44	42	51	47
	Max.	140	140.5	162.7	139
Duration of Asthma	**n**	135	576	44	135
	≥1 to <5 years	14 (10%)	60 (10%)	3 (7%)	17 (13%)
	≥5 to <10 years	20 (15%)	79 (14%)	7 (16%)	25 (19%)
	≥10 to <15 years	22 (16%)	113 (20%)	6 (14%)	14 (10%)
	≥15 to <20 years	14 (10%)	77 (13%)	8 (18%)	23 (17%)
	≥20 to <25 years	18 (13%)	68 (12%)	5 (11%)	15 (11%)
	≥25 years	47 (35%)	179 (31%)	15 (34%)	41 (30%)
	Mean	21.6	19.9	23.3	18.7
	SD	15.73	13.84	16.7	13.13
	Median	18	17	18	16
	Min.	1	1	3	1
	Max.	60	66	62	58
Airway Inflammation Characteristics:					
12 months prior to visit 1 elevated peripheral blood eosinophil count ≥300/uL	**Yes**	38 (27%)	397 (69%)	**Blood eosinophil inclusion criteria were assessed at visit 3 not visit 1, i.e. at the end of the run-in period not at screening in contrast to MENSA. So this information was not collected for patients who failed the randomisation criteria at the end of the run-in.**	
	No	88 (63%)	179 (31%)		
	Missing	14 (10%)	0		
At visit 1 elevated peripheral blood eosinophil count ≥150/uL	**Yes**	63 (45%)	477 (83%)		
	No	75 (54%)	86 (15%)		
	Missing	2 (1%)	13 (2%)		
Total number of exacerbations	**n**	135	576	44	135
	0	4 (3%)	0	10 (23%)	22 (16%)
	1	3 (2%)	1 (<1%)	8 (18%)	22 (16%)
	2	55 (41%)	245 (43%)	7 (16%)	23 (17%)
	3	27 (20%)	141 (24%)	3 (7%)	20 (15%)
	4	12 (9%)	76 (13%)	6 (14%)	25 (19%)
	>4	34 (25%)	113 (20%)	10 (23%)	23 (17%)
	Mean	3.7	3.6	2.9	3.1
	SD	3.09	2.58	2.79	3.1
	Median	3	3	2	3
	Min.	0	1	0	0
	Max.	28	21	10	16
Total number of exacerbations that required ER visits and/or hospitalisation	**n**	135	576	44	135
	0	92 (68%)	386 (67%)	34 (77%)	101 (75%)
	1	14 (10%)	89 (15%)	6 (14%)	17 (13%)
	2	13 (10%)	53 (9%)	2 (5%)	7 (5%)
	3	8 (6%)	20 (3%)	0	4 (3%)
	4	3 (2%)	9 (2%)	1 (2%)	3 (2%)

	>4	5 (4%)	19 (3%)	1 (2%)	3 (2%)
Total number of exacerbations that required hospitalisation	**n**	135	576	44	135
	0	106 (79%)	467 (81%)	39 (89%)	112 (83%)
	1	13 (10%)	63 (11%)	1 (2%)	13 (10%)
	2	8 (6%)	27 (5%)	3 (7%)	4 (3%)
	3	4 (3%)	12 (2%)	0	3 (2%)
	4	1 (<1%)	2 (<1%)	0	2 (1%)
	>4	3 (2%)	5 (<1%)	1 (2%)	1 (<1%)
Previously Administered Xolair:	**n**	137	576	44	135
	Yes	17 (12%)	75 (13%)	12 (27%)	45 (33%)
	No	120 (88%)	501 (87%)	32 (73%)	90 (67%)
Previously Failed on Xolair:	**n**	17	75	12	45
	Yes	16 (94%)	67 (89%)	12 (100%)	45 (100%)
	No	1 (6%)	8 (11%)	0	0
Screening:					
Pre-bronchodilator % Predicted Normal FEV_1 (%)	**n**	137	575	44	135
	Mean	59.6	56.7	63.1	57
	SD	15.19	15.48	20.57	18.1
	Median	60,6	57.2	67.2	56.8
	Min.	12	15	30	19
	Max.	106	98	112	100
Pre-bronchodilator FEV_1/FVC	**n**	138	575	44	135
	Mean	0.64	0.63	0.62	0.61
	SD	0.14	0.123	0.12	0.12
	Median	0.64	0.63	0.63	0.62
	Min.	0.3	0.3	0.4	0.3
	Max.	1	1	0.9	0.9
Baseline Blood Eosinophils (cells/µL)	**n**	138	576	45	135
	Geo. Mean	170	290	220	240
	Median	140	-	240	-
	Min.	0	0	0	0
	Max.	2100	3600	1500	2300

When looking at the MENSA trial, it can be seen that both sets of baseline characteristics are very similar. In MENSA, there were slight differences in the gender, where the run-in failure patient population had more female patients (69%). However, the ITT population had a more balanced patient population by gender with female patients being 57% of the total. This was not the case in the SIRIUS trial had a more balanced gender split.

In MENSA, there were larger differences in the airway inflammation characteristics with the proportion of patients with elevated peripheral blood eosinophil counts of ≥300 cells/µL in the 12 months prior to visit 1 representing 69% of patient in the ITT population compared to only 27% in the run-in failure population. Similarly, the percentage population of patients with a peripheral blood count of ≥150 cells/µL at visit 1 was higher in the ITT population (83%) compared to the run-in failure population (45%).

The exacerbation rates of the two sets of patients were very similar, including for those that required hospitalisation and/or emergency room visits. Again in MENSA, the baseline blood eosinophil levels had slight variations, as the ITT population had a mean of 290 cells/µL, and the run-in failure population had a mean of 170 cells/µL. There was no major difference in the SIRUS trial.

(D) In summary, both in MENSA and SIRIUS the majority of patients that withdrew during the run-in periods did so due to not meeting the continuation criteria (including eosinophil blood count, compliance) or withdrew due to reasons not related to their asthma (e.g. patients choice, asthma unrelated disease). In view of this, we do not believe that the generalisability of the MENSA and SIRIUS trial efficacy estimates to clinical practice are affected. Indeed, as would be expected in clinical practice, patients that were not compliant with their management, had confounding co-morbidities (e.g. abnormal cardiac or liver findings) and did not fulfil the asthma diagnostic criteria

(e.g. eosinophilic inflammation, persistent airway obstruction, not optimised standard of care) would not be eligible for add-on mepolizumab therapy as was the case with the patients listed above.

A18. Please clarify why 9 patients in the DREAM trial were withdrawn at the "investigator's discretion" (Patient flow, Page 61 of the company's submission).

Table 20 below outlines the reason for the patient's withdrawal at the investigators discretion. The listing includes 10 rather than 9 subjects since there was an additional subject who was randomised in error but who was also withdrawn at investigator discretion prior to receiving treatment.

Table 20: Listing of Reasons for Screen Failure and Run-in Failure Subjects that Withdrew Due to 'Investigator Discretion' (DREAM)

Investigation number	Subject	Date of failure	Failure type	Reason for failure
068312	2078	20th August 2010	Screen	Investigator discretion, specify: Patient was exacerbating at time of screening. Decision was made to possibly screen at a later date.
068854	2491	23rd March 2010	Run-in	Investigator discretion: Unstable sinusitis affecting asthma requiring varying doses of antibiotics and oral steroids.
069960	1263	11th August 2010	Run-in	Investigator discretion: asthma patient is unstable, also patient is emotionally unstable because of family issues. Investigator decided not to randomise and remove patient from study.
070207	205	2nd June 2010	Run-in	Investigator discretion: Laboratory result.
070210	237	17th Feb 2010	Run-in	Investigator discretion: Patient not interested.
070390	1127	21st Oct 2010	Run-in	Investigator discretion: Pharmacy at site unable to manufacture infusion at required visit time. Recruitment had closed and any further delay not possible. Hence patient not randomised.
070929	702	25th July 2010	Screen	Investigator discretion, specify: Inclusion criteria 9 not fulfilled
070931	681	13th July 2010	Screen	Investigator discretion, screen: FEV1 less than 1L
071311	3306	31st August 2010	Run-in	Investigator discretion: A patient recalled ICF on family circumstances.
075023	2702	19th August 2010	Run-in	Investigator discretion: Subject has not been on high dose ICS for >12 months.

Note: Five of the patients above had more than one reason for withdrawal, which included asthma unrelated disease (e.g. hepatitis, upper or lower respiratory tract infection, ECG abnormalities), misdiagnosis of asthma and asthma exacerbation.

As discussed in question A17, in view of the above reasons for withdrawal we do not believe that the generalisability of the DREAM trial efficacy estimates to clinical practice are affected.

A19. Please clarify whether the continuation rules for treatment with mepolizumab in COSMOS and COLUMBA were consistent with the recommendations in the SmPC for mepolizumab. (Page182 of the company's submission) Please clarify if the continuation rules in these trials differ from the continuation rule used in the company's economic model.

Yes, the continuation rules for treatment with mepolizumab in COSMOS and COLUMBA were consistent with the recommendations in the SmPC.

In section 4.13 (Long-term efficacy of mepolizumab therapy) we state: 'The draft SmPC by the EMA states 'the need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations'. In the clinical trial program none of the outcomes measures were found to be predictive of a future response to mepolizumab therapy. In current clinical practice, patients are reviewed on a regular basis by physicians (2-4 times per year) and nurses (at administration appointments). Thus, a holistic patient assessment of treatment goals (i.e. exacerbation reduction, OCS dose reduction, quality of life, asthma control, etc) at those review time points, evaluating risk/benefit of mepolizumab therapy for each individual patient, seems clinically most appropriate.'

Both OLE studies are consistent with the above rational. As expected in a clinical trial of an investigational medicine, both OLEs also include a range of more specific reasons for withdrawal (please see OLE CSRs). These withdrawal criteria were unlikely to be relevant in clinical practice and were not included in the SmPC.

COSMOS was a 52 week study which demonstrated the continual benefit of add-on mepolizumab therapy for one year beyond the original 32 and 24 week studies (MENSA and SIRIUS). The withdrawal rate was low at 10% which supports the positive benefit risk of mepolizumab in patients with severe refractory eosinophilic asthma for at least 52 weeks. This evidence therefore is consistent with the SmPC recommendation and in line with good clinical practice of current patient management.

COLUMBA is a long term study of more than 3 years duration where 'subjects are continuing to receive mepolizumab SC injections approximately every 4 weeks until either: 1) the risk/benefit profile is no longer positive in the opinion of the investigator or; 2) the subject's physician withdraws the subject or; 3) the subject withdraws consent or; 4) the sponsor discontinues development of mepolizumab or; 5) the sponsor discontinues the study in the relevant participating country or; 6) mepolizumab becomes commercially available in the relevant participating country'.
In this study, the withdrawal criteria outlined above were evaluated in the clinic approximately every 4 weeks, to assess adverse events and asthma status. However, at a minimum, each subject has a yearly assessment of risk/benefit of mepolizumab therapy performed by the investigator. The withdrawal rate was low at 6% at the interim data cut off point (28th February 2014) which supports the positive benefit risk of mepolizumab in patients with severe refractory eosinophilic asthma who at a minimum had a yearly review. This evidence therefore is consistent with the SmPC recommendation and in line with good clinical practice of current patient management to perform at least a yearly assessment.

When assessing cost effectiveness, the patient was withdrawn from the analysis if they demonstrated a worsening in the exacerbation rate. This was selected as a pragmatic approach to identify those patients with the least capacity to benefit from mepolizumab. Patients demonstrating no change in the level of exacerbations were assumed to have continued treatment to reflect those patients on oral corticosteroids for whom the primary treatment objective was to reduce OCS exposure whilst maintaining asthma control and also account for patients who may experience additional benefit, such as HRQL or symptomatic improvement, irrespective of exacerbation reduction. However the minimal required frequency for patient assessment was 1 year, which was consistent with the SmPC.

However we believe this represents a conservative approach, as in clinical practice patients may be reviewed at an earlier time point and taking into account a broader range of factors.

A20. Please clarify the definition of standard care used in each of the omalizumab and mepolizumab trials, including details of the treatments given.

Mepolizumab RCTs:

In all the phase IIb/III trials, patients had to be uncontrolled despite appropriate therapy (standard of care), including **high dose ICS** plus **additional controller therapy**, i.e., treatment at Step 5/6 and Step 4/5 according to the National Heart, Lung, and Blood Institute Guidelines for the Diagnosis and Treatment of Asthma [NHLBI, 2008] and the Global Initiative for Asthma guidelines [GINA, 2008], respectively. This is equivalent to **step 4 and 5 of the BTS/SIGN guidance** relevant for UK clinical practice.

(a) DREAM: 'Subjects with a well-documented requirement for regular treatment with high dose ICS (i.e., ≥880 µg/day fluticasone propionate or equivalent daily), with or without maintenance OCS, in the 12 months prior to Visit 1. Subjects with a well-documented requirement for controller medication, e.g., LABA, leukotriene receptor antagonist or theophylline in the 12 months prior to Visit 1'.

Summaries of asthma medications taken before run-in and during treatment, started during the study and taken post-treatment are presented by respiratory medication class in the DREAM CSR Source Data Table 5.24, Table 5.25, Table 5.26 and Table 5.27, respectively.

(b) MENSA: '...documented requirement for regular treatment with high-dose inhaled corticosteroid (ICS) in the 12 months prior to Visit 1 [ages ≥18: ≥880 mcg/day fluticasone propionate (FP) (ex-actuator) or equivalent daily; ages 12-17 ≥440 mcg/day FP (ex-actuator) or equivalent] with or without maintenance oral corticosteroids (OCS) and require additional controller medication besides ICS, e.g., long-acting beta-2 receptor agonist (LABA), leukotriene receptor antagonist (LTRA) or theophylline in the past 12 months for at least 3 successive months.'

Summaries of asthma medications taken before run-in and during treatment, started during the study and taken post-treatment are presented by respiratory medication class in the MENSA CSR Source Data Table 5.28, Table 5.29, Table 5.30 and Table 5.31, respectively.

(c) SIRIUS: '...documented requirement for regular treatment with maintenance systemic corticosteroids (5.0 to 35 mg/day prednisone or equivalent) and high-dose inhaled corticosteroids (ICS) (ages ≥18: ≥880 mcg/day fluticasone propionate [FP] [ex-actuator] or equivalent; ages 12-17 ≥440 mcg/day FP [ex-actuator] or equivalent) in the 6 months prior to Visit 1 were eligible. Subjects had to also be receiving current treatment with an additional controller medication for at least 3 months or documentation of having used and failed an additional controller medication for at least 3 successive months during the prior 12 months.

Summaries of asthma medications taken before run-in and during treatment, started during the study and taken post-treatment are presented by respiratory medication class in the SIRIUS CSR Source Data Table 5.24, Table 5.26, Table 5.27 and Table 5.28, respectively.

Records of medication taken were source verified by the GSK monitor at the site. Two subjects in DREAM and 9 subjects in MENSA (see response to Question 94c) were excluded from the per protocol analyses due incomplete records over the 12 months prior to the study of continuous high dose ICS use.

Records of treatment taken prior to run-in show that 95% of subjects in DREAM and 97% in DREAM were receiving ICS/LABA at baseline. A further 38% in MEA112997 and 57% in DREAM were also receiving, in addition to an ICS/LABA, a long-acting anticholinergic, a leukotriene receptor antagonist, xanthine and nedocromil or cromolyn sodium.

Thirty one percent of subjects in MEA112997 and 24% of subjects in MEA115588 were also receiving continuous OCS treatment. Mean (range) baseline maintenance OCS daily dose for subjects receiving OCS treatment in MEA112997 was 17.4 (3–160) mg/day and 13.2 (1-80) mg/day in DREAM. All subjects in SIRIUS were reported as receiving high-dose (i.e. ≥880 µg/day FP or equivalent) ICS for 12 months prior to screening (appendix 21 Table 5.19). All except one subject in

SIRIUS were all using ICS/LABA prior to study and 60% were also receiving a long-acting anticholinergic, a leukotriene receptor antagonist, xanthine and nedocromil or cromolyn sodium in addition to ICS/LABA

Mepolizumab OLEs:

(d) COSMOS: patients in the open label extension (OLE) studies directly entered the OLE after completing MENSA and SIRIUS, and thus fulfilled the above inclusion criteria and definition of standard of care.

Summaries of asthma medications taken during treatment, started during the study and taken post-treatment are presented by respiratory medication class in the CSR Source Data: Table 5.22, Table 5.23 and 5.24, respectively.

(e) COLUMBA: patients entered this OLE study after a minimum break of 10 month after exiting DREAM. All subjects were required to be on at least one asthma controller medication for at least 12 weeks prior to study start. The most common class of asthma controller medication was ICS/LABA combination with approximately 80% of subjects reporting taking this medication.

Summaries of asthma medications taken before run-in, during treatment, started during the study and taken post-treatment are presented by respiratory medication class in the CSR Source Data Table 5.28, Table 5.29, Table 5.30 and 5.31, respectively.

Omalizumab studies:

The definition of standard of care as reported in the extracted omalizumab RCTs and non-RCTs is provided below in Table 21 and Table 22 respectively, by study (identified in Table 7 page 35 [RCTs] and Table 8 [non-RCTs] page 36).

Table 21: Definition of standard of care from the included omalizumab RCT studies

Trial	Definition of standard of care
Holgate, 2004	Required ≥1000 mg/day fluticasone for symptom control (all patients were switched to inhaled fluticasone during the run-in period). SABAs were allowed as needed, along with continued use of LABAs. Note that patients taking theophylline or anti-leukotrienes, or with a history of anaphylaxis, recent near-fatal asthma, respiratory infection within 4 weeks of the study, parasitic infection or an elevated serum total IgE for reasons other than atopy were excluded.
Humbert, 2005	Severe persistent asthma requiring regular treatment with >1000 µg/day BDP or equivalent and LABA (GINA step 4 treatment). Additional asthma medications, taken regularly from >4 weeks prior to randomisation were permitted, including theophyllines, oral β_2-agonists and antileukotrienes. Maintenance oral corticosteroids (maximum 20 mg/day) were permitted providing at least one of the exacerbations in the previous 12 months had occurred while on this therapy.
Sthoeger, 2007	Regular treatment with inhaled corticosteroids > 1000 µg/day of beclomethasone dipropionate (or equivalent) and LABA (GINA 2002 step 4 treatment)
Humbert, 2008	High-dose ICS plus a LABA with additional controller medication as necessary, as per Humbert 2005
Hanania, 2011	High-dose ICS was a minimum dose of 500 mcg of fluticasone dry-powder inhaler twice daily or its similar exvalve dose for at least 8 weeks before screening. LABA treatment could either be salmeterol, 50 µg twice daily, or formoterol, 12 µg twice daily, for at least 8 weeks before screening
Hanania, 2013	High dose ICS plus LABA
Bardelas, 2012	Prescription for at least a medium-dose ICS plus LABA(fluticasone 250 µg/ salmeterol 50 µg one inhalation or budesonide 160 µg/formoterol 4.5 µg two inhalations twice daily); a medium-dose ICS plus either a LTRA, theophylline, or zileuton for ≥3 months
Busse, 2001	Treatment with 420 to 840 µg/day of beclomethasone dipropionate (BDP) or its equivalent ICS for ≥3 months prior to randomization
Finn,	Moderate-to-high doses of ICSs (based on Busse 2001)

2003	
Lanier, 2003[66]	Treatment with 420 to 840 µg/day of beclomethasone dipropionate (BDP) or its equivalent ICS for ≥3 months prior to randomization
Garcia, 2013	Daily high-dose ICS treatment (>1,000 m g beclomethasone dipropionate or equivalent per day) plus a LABA with or without maintenance oral corticosteroid
Zakaria, 2013	High-dose ICS and LABA
Chanez, 2010	High dose ICS >1000 mg beclometasone dipropionate or equivalent and an inhaled LABA
Massanari, 2010	ICS
Ohta, 2009	Treatment with beclomethasone dipropionate chlorofluorocarbon (CFC)- containing metered-dose inhaler at ≥800 mg/day (or equivalent), and one or more of the following additional controller medications recommended as step 3 and step 4 treatments LABA, sustained-release theophylline, leukotriene receptor antagonist (LTRA), oral corticosteroid).
Ayres, 2004	Receiving ≥400 µg/day (adolescent, age <18 years) or ≥800 µg/day (adult) inhaled beclomethasone dipropionate (BDP) (or equivalent).
Niven, 2008	≥400 µg/day (adolescent, age <18 years) or ≥800 µg/day (adult) inhaled beclomethasone dipropionate (BDP) (or equivalent).
Bousquet, 2011	≥800 µg BDP (beclomethasone dipropionate) or equivalent plus a LABA during the 3 years prior to screening. Additional asthma medications (e.g. oral corticosteroids [OCS], theophyllines, cromones, anti-leukotrienes) were allowed if established >4 weeks prior to randomization. Short-acting b2-agonists were permitted as rescue medication
Siergiejko, 2011	High-dose ICS (41000 mg beclomethasone dipropionate [BDP]/day or equivalent) and a LABA
Hoshino, 2012	High-dose ICS plus a LABA. Other asthma medications, including theophylline and anti-leukotrienes taken regularly from ≥8 weeks prior to randomization, were permitted; maintenance oral corticosteroids (maximum prednisolone 20 mg/day) were permitted providing at least one exacerbation had occurred in the previous year
Rubin, 2012	At least, ICS (≥500 µg/day of fluticasone equivalent) + LABA
Solèr, 2001	Treatment with ICS in doses equivalent to 500–1,200 mg of beclomethasone dipropionate (BDP) per day for ≥3 months prior to randomiSation and use of b2-adrenoceptor agonists on an as-needed or regular basis
Buhl, 2002	Treatment with ICS in doses equivalent to 500–1,200 mg of beclomethasone dipropionate (BDP) per day for ≥3 months prior to randomization and use of b2-adrenoceptor agonists on an as-needed or regular basis
Buhl, 2002	Treatment with inhaled corticosteroids in doses equivalent to 500–1,200 mg of beclomethasone dipropionate (BDP) per day for ≥3 months prior to randomization and use of b2-adrenoceptor agonists on an as-needed or regular basis
Milgrom, 1999	Daily use of a β-agonist bronchodilator as a rescue medication
NCT00670930	High dose ICS(≥800µg per day BDP or equivalent) and a regular long acting beta-agonist for at least 3 months prior to screening
Bousquet, 2004	Moderate to high dose ICS (pooled analysis of Busse 2001 and Soler 2001)
Busse, 2013	ICS with or without other controller medications
Vignola, 2004	Receiving ≥400 µg/day of inhaled corticosteroid (ICS)

ICS Inhaled corticosteroids; LABA Long acting β_2-agonists; SABA Short acting β_2-agonists; OCS oral corticosteroids

Table 22: Definition of standard of care from the included omalizumab non-RCT studies

Study	Definition of Standard of care
Velling 2011	>1000 µg/day beclomethasone dipropionate or equivalent and LABA, OCS permitted
Vennera 2012	Ongoing treatment with high doses of ICS in association with LABA OCS permitted
Rottem 2012	High dosages of ICS in association with long-acting β2-agonists, OCS permitted

Korn 2010	ICS, LABAs, oral corticosteroids, sustained-release theophylline, or leukotriene receptor antagonists
Korn 2009	High doses ICS and LABAs, OCS permitted
Llano 2013	NR
Chivato 2009	NR
Braunstahl 2013	NR
Van Nooten 2013	High dose ICS (>1000mg beclomethasone) and a LABA
Braunstahl 2013	ICS/LABA/SABA/LAMA/leukotriene inhibitors/OCS permitted
Grimaldi-Bensouda 2013	Treatment with 1,000 mg beclomethasone equivalent, one LABA, and at least one of the following: (1) 5 mg prednisone equivalent per day for at least 6 months; (2) at least three courses of oral corticosteroids over 1 year; or (3) two courses of oral corticosteroids over 1 year
Tajiri 2014	Concomitant use of LABA, leukotriene receptor antagonists, or theophylline, in addition to high-dose ICSs or concomitant oral corticosteroids
Molimard 2010	Majority of patients were receiving regular treatment with ICS (97.6%) and LABA (95.8%) either as monotherapy or ICS/LABA combination therapy
Lafeuille 2012	ICS/LABA required, OCS permitted
Barnes 2013	ICS/LABA/OCS
Costello 2011	ICS/LABA NR OCS permitted
Zietkowski 2011	All patients used inhaled SABAs (as rescue medication), inhaled long-acting b2 agonists, high-doses of inhaled steroids (without oral steroids), and leukotriene receptor antagonists.
Brusselle 2009	ICS/LABA required, OCS permitted
Kulichenko 2009	High dose ICS
Lafeuille 2013	ICS/LABA required, OCS permitted
Kupyrs-Lipinska 2014	Not reported
Lafeuille 2012	ICS/LABA required, OCS permitted
Kuo 2014	NR
Pereira 201	NR, OCS permitted
Britton 2012	NR
Barnes 2012	NR
Zamora 2013	NR
Saji 2014	NR

ICS Inhaled corticosteroids; LABA Long acting β_2-agonists; SABA Short acting β_2-agonists; OCS oral corticosteroids

A21. Please clarify why patients in COSMOS and COLUMBA were only selected if they continued with controller therapy (page 151 of the company's submission) and what type of controller therapy was eligible?

As we know, there are current controller therapies available which have been shown to be effective in controlling asthma symptoms and airway inflammation in the majority of patients. However, a proportion of these asthma patients remain uncontrolled despite appropriate therapy at step 4 and 5 of the BTS/SIGN guidance (high dose ICS + additional controllers, including LABA, LTRA, LAMA, etc +/- maintenance OCS). This severe uncontrolled, eosinophilic population suffers from persistent symptoms and acute exacerbations of their asthma (i.e. severe refractory eosinophilic asthma patients).

Mepolizumab has been developed as an add-on therapy for use with patients already on controller medications. It was therefore a requirement for all patients within the trials to have been on controller therapies for the duration of the trials to provide a population consistent with the SmPC and most representative of those who are likely to receive mepolizumab in clinical practice and aligned with national guidance.

Controller therapies could have included ICS, LABA, LTRA, LAMA, theophylline or OCS based on the NHLBI and GINA guidelines (aligned with step 4 & 5 of the BTS/SIGN). It should also be noted that within the COLUMBA trial, as there was a treatment free period after DREAM, the requirement was for patient's to have been on these controller medications for at least 12 weeks before the start of the study.

A22. Please clarify whether the company expect that monitoring (i.e. of all patients being given mepolizumab) or measuring (e.g. where response to therapy has decreased in a given patient) of antibody resistance will be necessary in patients in clinical practice?

We do not expect that monitoring and measuring of antibody resistance will be required in patients treated with add-on mepolizumab in addition to the general safety follow up of spontaneous event reporting, and it is not a requirement in the SmPC. GSK has ongoing long-term safety studies (COLUMBA, Study 201312) to continue to collect immunogenicity data to gain further understanding.

Mepolizumab has low immunogenic potential (6% with mepolizumab 100 mg SC and 2% with all IV doses combined) based on both low incidence and low titre of anti-drug antibodies and neutralising antibodies; the data demonstrated a low risk for loss of efficacy associated with AEs and/or altered PK/PD (see Integrated Summary of Immunogenicity, m5.3.5.3).

To date, there have been no apparent clinical or pharmacokinetic/pharmacodynamic findings associated with anti-mepolizumab antibodies in any subjects. Both incidence and titre data available from completed studies reveal no apparent association with adverse events, loss of disease control and/or altered pharmacokinetic or pharmacodynamic profiles. Overall, the findings to date indicate low risks and/or concerns associated with the immunogenicity profile of mepolizumab.

This is consistent with the SmPC that states: 'Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment. In the placebo-controlled trials, 15/260 (6%) of subjects treated with 100 mg dose subcutaneously developed anti-mepolizumab antibodies after having received at least one dose of mepolizumab. Neutralising antibodies were detected in one subject. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level.'

Meta-analyses

A23. Priority Question. Please provide baseline and efficacy data for DREAM in the company's proposed population and ITT populations, for each study arm.

Please, see section A9, Table 2 for clinical efficacy data for each study with the original ITT populations and the two company proposed populations side by side for DREAM, MENSA, SIRIUS.

The DREAM results for the proposed population including and excluding patients on maintenance OCS and with < 4 exacerbations align with the MENSA results and supports the GSK proposed population. Mepolizumab 75mg IV showed an improved reduction in rate of exacerbations vs SOC in the GSK proposed population (64%,$p<0.001$) compared to the ITT population (48%, $p<0.001$). This trend was consistent for all doses studied in DREAM (250mg: 69%, $p<0.001$ vs placebo 39%, $p<0.001$ and 750mg: 63%, $p<0.001$ vs placebo 52%, $p<0.001$), including rate of exacerbations requiring ED visits and/or hospitalisations (see table A9 above).

DREAM baseline demographics for the ITT populations can be found in section 4.9 and appendix 8.3 of the main submission. The baseline characteristics for the proposed populations in DREAM are below in Table 23. As previously confirmed in MENSA, the ITT and GSK populations were not dramatically different at baseline. As expected from the selection criteria of the GSK proposed population (blood eosinophil count ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or maintenance OCS use) baseline eosinophil levels, OCS use and mean

exacerbation rate in the previous year were higher in the GSK proposed population, reflective of the proposed population's increased burden of disease.

Table 23: Baseline Characteristics (DREAM, Proposed Populations)

		GSK Proposed Population excluding mOCS users with <4 exacerbations					GSK Proposed Population				
Characteristic	**Analysis**	Placebo	Mepo 75mg IV	Mepo 250mg IV	Mepo 750mg SC	Total	Placebo	Mepo 75mg IV	Mepo 250mg IV	Mepo 750mg SC	Total
Age (yrs)	**n**	32	39	29	34	134	56	54	51	51	212
	Mean	47.3	50.9	49.9	46.0	48.6	49.4	50.7	50.2	48.2	49.6
	SD	11.86	10.71	10.61	12.53	11.50	10.92	10.58	11.66	11.87	11.22
	Median	48.5	51.0	51.0	48.0	50.0	52.0	50.0	51.0	49.0	51.0
	Min.	23	24	22	19	19	23	24	22	19	19
	Max.	67	69	66	64	69	67	69	73	66	73
Sex	**n**	32	39	29	34	134	56	54	51	51	212
	Female	22(69%)	28(72%)	18(62%)	26(76%)	94(70%)	34(61%)	39(72%)	26(51%)	36(71%)	135(64%)
	Male	10 (31%)	11 (28%)	11(38%)	8(24%)	40(30%)	22(39%)	15(28%)	25(49%)	15(29%)	77(36%)
Ethnicity	**n**	32	39	29	34	134	56	54	51	51	212
	Hispanic or Latino	3(9%)	1(3%)	1(3%)	4(12%)	9(7%)	5(9%)	4(7%)	1(2%)	6(12%)	16(8%)
	Not Hispanic or Latino	29(91%)	38(97%)	28(97%)	30(88%)	125(93%)	51(91%)	50(93%)	50(98%)	45(88%)	196(92%)
Weight (kg)	**n**	32	39	29	34	134	56	54	51	51	212
	Mean	80.1	74.8	81.4	77.8	78.2	79.9	75.3	82.7	81.2	79.7
	SD	17.97	15.46	18.03	18.96	17.54	17.03	15.56	17.56	18.43	17.25
	Median	79.4	75.0	85.1	74.5	76.6	78.3	76.0	85.0	78.0	78.0
	Min.	53	45	52	45	45	53	45	52	45	45
	Max.	125	120	113	118	125	125	120	125	120	125
Duration of Asthma	**n**	32	39	29	34	134	56	54	51	51	212
	≥1 to <5 years	3(9%)	4(10%)	2(7%)	4(12%)	13(10%)	8(14%)	6(11%)	4(8%)	6(12%)	24(11%)
	≥5 to <10 years	4(13%)	8(21%)	5(17%)	6(18%)	23(17%)	11(20%)	10(19%)	9(18%)	8(16%)	38(18%)
	≥10 to <15 years	8(25%)	7(18%)	5(17%)	1(3%)	21(16%)	12(21%)	8(15%)	8(16%)	4(8%)	32(15%)
	≥15 to <20 years	1(3%)	2(5%)	3(10%)	6(18%)	12(9%)	1(2%)	5(9%)	3(6%)	7(14%)	16(8%)
	≥20 to <25 years	7(22%)	6(15%)	2(7%)	6(18%)	21(16%)	8(14%)	7(13%)	8(16%)	8(16%)	31(15%)
	≥25 years	9(28%)	12(31%)	12(41%)	11(32%)	44(33%)	16(29%)	18(33%)	19(37%)	18(35%)	71(33%)
Airway Inflammation Characteristics:											
At visit 1 or documented in the previous 12 months elevated peripheral blood eosinophil count ≥300/uL	**Yes**	23(72%)	30(77%)	23(79%)	28(82%)	104(78%)	38(68%)	37(69%)	37(73%)	37(73%)	149(70%)
	No	6(19%)	4(10%)	5(17%)	1(3%)	16(12%)	12(21%)	8(15%)	12(24%)	7(14%)	39(18%)
	Unknown	3(9%)	5(13%)	1(3%)	5(15%)	14(10%)	6(11%)	9(17%)	2(4%)	7(14%)	24(11%)
Baseline OCS daily dose (prednisolone equivalent) [2]	**n**	13	20	11	18	62	37	35	33	35	140
	<7.5 mg/day	2(15%)	2(10%)	1(9%)	2(11%)	7(11%)	8(22%)	5(14%)	7(21%)	5(14%)	25(18%)
	≥7.5-<15 mg/day	8(62%)	8(40%)	4(36%)	7(39%)	27(44%)	16(43%)	13(37%)	14(42%)	15(43%)	58(41%)
	≥15-<30 mg/day	2(15%)	5(25%)	1(9%)	7(39%)	15(24%)	7(19%)	9(26%)	5(15%)	12(34%)	33(24%)
	≥30 mg/day	1(8%)	5(25%)	5(45%)	2(11%)	13(21%)	6(16%)	8(23%)	7(21%)	3(9%)	24(17%)
	Mean	14.5	21.2	37.0	18.1	21.7	15.6	19.2	20.7	15.6	17.7
	SD	14.39	17.18	45.51	16.99	24.70	12.66	14.72	28.98	13.29	18.33
	Median	10.0	13.8	20.0	13.7	10.0	10.0	12.5	10.0	10.0	10.0
	Min.	5	5	5	5	5	5	5	3	5	3
	Max.	60	60	160	80	160	60	60	160	80	160
Total number of exacerbations	**n**	32	39	29	34	134	56	54	51	51	212
	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0	0	0

	2	0	0	0	0	0	8(14%)	8(15%)	10(20%)	8(16%)	34(16%)
	>2	32(100%)	39(100%)	29(100%)	34(100%)	134(100%)	48(86%)	46(85%)	41(80%)	43(84%)	178(84%)
	Mean	8.0	6.7	6.0	6.0	6.7	5.7	5.6	4.5	4.8	5.2
	SD	6.55	4.66	3.07	3.60	4.70	5.60	4.40	2.89	3.37	4.24
	Median	5.5	5.0	5.0	4.5	5.0	4.0	4.0	4.0	4.0	4.0
	Min.	4	4	4	4	4	2	2	2	2	2
	Max.	30	25	15	20	30	30	25	15	20	30
Total number of exacerbations that required hospitalisation	**0**	24(75%)	31(79%)	20(69%)	28(82%)	103(77%)	43(77%)	45(83%)	39(76%)	41(80%)	168(79%)
	1	3(9%)	5(13%)	6(21%)	4(12%)	18(13%)	6(11%)	5(9%)	9(18%)	7(14%)	27(13%)
	2	0	2(5%)	2(7%)	0	4(3%)	2(4%)	3(6%)	2(4%)	1(2%)	8(4%)
	>2	5(16%)	1(3%)	1(3%)	2(6%)	9(7%)	5(9%)	1(2%)	1(2%)	2(4%)	9(4%)
Pre-bronchodilator % Predicted Normal FEV1 (%)	**n**	32	39	29	34	134	56	54	51	51	212
	Mean	56.9	56.6	59.2	60.0	58.1	55.7	57.1	59.6	59.3	57.9
	SD	15.67	18.15	15.59	19.00	17.15	15.62	17.95	18.12	18.77	17.56
	Median	55.3	52.3	58.1	59.1	57.3	54.5	58.7	59.2	58.5	57.5
	Min.	34	18	34	25	18	26	18	22	24	18
	Max.	90	94	86	107	107	90	94	99	108	108
Baseline Blood Eosinophils (U/mL)	**n**	32	39	29	34		56	54	51	51	
	Geo. Mean	450	400	510	480		450	380	440	430	
	Median	430	400	450	420		460	370	400	380	
	Min.	200	200	200	200		200	200	200	200	
	Max.	2300	1500	4100	2000		2300	1500	4100	2000	
Baseline Total IgE (U/mL)	**n**	32	39	29	34	134	56	54	51	51	212
	Geo. Mean	209.72	263.13	160.10	152.23	194.82	194.03	200.27	164.92	118.72	167.13
	Std Logs	1.271	1.330	1.542	1.239	1.347	1.361	1.415	1.525	1.185	1.383
	Median	168.00	325.00	159.00	196.00	215.00	181.50	245.50	140.00	126.00	164.50
	Min.	18.0	13.0	5.0	15.0	5.0	4.0	13.0	5.0	7.0	4
	Max.	2934.0	4114.0	1941.0	803.0	4114.0	3047.0	4114.0	9130.0	803.0	9130.0
Baseline ACQ-5 Mean Score	**n**	32	38	29	33	132	56	52	50	50	208
	Mean	2.7	2.4	2.5	2.8	2.6	2.6	2.4	2.7	2.5	2.5
	SD	1.20	1.29	1.33	1.35	1.29	1.19	1.18	1.33	1.34	1.25
	Median	2.8	2.5	2.8	2.8	2.8	2.4	2.5	2.8	2.6	2.6
	Min.	0	0	0	0	0	0	0	0	0	0
	Max.	5	5	5	6	6	5	5	5	6	6
Baseline EQ5D Total Score	**n**	24	15	22	17		56	54	51	51	
	Mean	0.78	0.77	0.73	0.68		0.80	0.73	0.74	0.71	
	SD	0.209	0.145	0.254	0.319		0.180	0.226	0.191	0.280	
	Median	0.76	0.73	0.77	0.76		0.78	0.74	0.74	0.76	
	Min.	0.2	0.6	0.1	-0.00		0.2	0.1	0.1	-0.1	
	Max.	1.0	1.0	1.0	1.0		1.0	1.0	1.0	1.0	

A24. Priority Question. Please provide a meta-analysis of MENSA and DREAM (page 114 of the company's submission) compared with standard of care in the company's proposed population, and in the proposed population excluding maintenance oral corticosteroids (mOCS) users. Please provide these analyses for all outcomes (including clinically significant exacerbations, hospitalisations and QoL). Please also provide a sensitivity analysis including SIRIUS.

Table 24 below summarises the meta-analysis results for questions A5 and A24.

Overall, the results support the GSK proposed population. The meta-analysis of MENSA and DREAM as well as the sensitivity analysis including SIRIUS show consistently that in both the GSK proposed population and in the GSK proposed population excluding OCS users with <4 exacerbations a clinically and statistically significant reduction in the rate of exacerbations (all doses: 61%, p<0.001 & 67%, p<0.001 [for MENSA and DREAM] and 53%, p<0.001 & 61%, p<0.001 [for the sensitivity analysis including SIRIUS], respectively) as well as rate of exacerbation requiring ED visits and/or hospitalisations is achieved (where possible to perform, see Table 25). This reduction was improved in the GSK proposed population compared to the ITT population (all doses: 48%, p<0.001) and supports the individual DREAM, MENSA and SIRIUS results in table 2, question A9.

As expected the reduction in exacerbations for adult subjects with ≥150cells/μL on maintenance OCS with <4 exacerbations in the meta-analysis is less compared to the GSK proposed population excluding mOCS users with <4 exacerbations (Table 24). Nevertheless, all reductions are clinically significant and by combining the results and thus increasing the number of subjects looked at in this meta-analysis the reduction in rate of exacerbations becomes statistically significant. Thus, in addition to the clinical and ethical argument of equity this further supports the inclusion of this high burden population in the NICE reimbursement population.

Both in the GSK proposed population and in the GSK proposed population excluding OCS users with <4 exacerbations a clinically and statistically significant (MCID=0.5) improvement in asthma control (ACQ) can be observed when combining DREAM, MENSA and SIRIUS results (all doses: -0.59, p<0.001 & -0.76, p<0.001, respectively) compared to the ITT population (all doses: -0.29, p<0.001). Moreover, as measured by the SGRQ, there was a large clinically and statistically significant (MCID=4) improvement in quality of life in the combined analysis of MENSA and SIRIUS (see note 3 in table) by -7.7 (p<0.001) and -10.1 (p<0.001), respectively.

Subjects with ≥150cells/μL on maintenance OCS with <4 exacerbations on all doses achieved a statistically significant improvement in asthma control (ACQ) by 0.46 (p=0.002, MCID 0.5) and a clinically significant improvement in quality of life (SGRQ) by -4.3 units (p=0.093). However, the results have to be reviewed in context of the fact that the number of subject in this analysis was small (SGRQ subjects: Pbo n=49, all doses n=67; ACQ subjects: Pbo n 43, all doses n 92).

In summary, the meta-analysis results support the individual results seen in DREAM, MENSA and SIRIUS for the GSK proposed population. Indeed, the GSK proposed population showed additional benefit from add-on mepolizumab therapy compared to

the ITT population when comparing the meta-analysis results. This is in addition to the fact that this population of severe refractory eosinophilic asthmatics was selected for its increased burden of disease at baseline: with ≥150cells/μL blood eosinophils despite high dose steroid therapy (ICS and/or mOCS), with an increased risk of morbidity and mortality from ≥4 exacerbations in the previous year and the increased risk of short- and long-term side effects from maintenance OCS treatment. Therefore, in consideration of NHS resources we have identified a population of patients supported by clinical data that is readily identifiable in UK clinical practice and supported by UK clinicians in our advisory boards and is cost effective to the NHS (see questions B6 and B8).

Table 24: Meta-analysis results of MENSA and DREAM plus sensitivity analysis including SIRIUS compared with standard of care in the GSK proposed population (severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/μL at initiation of treatment; with ≥4 exacerbations in the previous year or dependency on systemic corticosteroids), the proposed population excluding maintenance oral corticosteroid (mOCS) users with <4 exacerbations and (answers to A5) severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/μL at initiation of treatment and dependency on systemic corticosteroids with <4 exacerbations in the previous year.

		ITT population[2]			GSK Proposed Population excluding mOCS users with <4 exacerbations[1]						GSK Proposed Population[1]						Subjects with ≥150cells/μL Baseline Blood Eosinophils on Maintenance OCS with <4 Exacerbations in Past Year[1]					
		Meta-analysis of DREAM and MENSA			Meta-analysis of DREAM and MENSA			Meta-analysis of DREAM, MENSA plus SIRIUS			Meta-analysis of DREAM and MENSA			Meta-analysis of DREAM, MENSA plus SIRIUS			Meta-analysis of DREAM and MENSA			Meta-analysis of DREAM, MENSA plus SIRIUS		
		Pbo	75mg IV / 100mg SC	All Doses	Pbo	75mg IV / 100mg SC	All Doses	Pbo	75mg IV / 100mg SC	All Doses	Pbo	75mg IV / 100mg SC	All Doses	Pbo	75mg IV / 100mg SC	All Doses	Pbo	75mg IV / 100mg SC	All Doses	Pbo	75mg IV / 100mg SC	All Doses
Rate of Clinically Significant Exacerbations	n	346	538	846	77	141	204	92	163	226	120	197	299	168	251	353	43	56	95	76	88	127
	Rate ratio		0.51	0.53		**0.35**	**0.33**		**0.42**	**0.39**		**0.41**	**0.39**		**0.50**	**0.47**		**0.55**	**0.50**		**0.64**	**0.59**
Comparison vs placebo	95% CI		0.42, 0.62	0.44, 0.62		0.25, 0.50	0.24, 0.46		0.30, 0.57	0.29, 0.51		0.31, 0.55	0.30, 0.50		0.40, 0.64	0.38, 0.58		0.32, 0.92	0.33, 0.77		0.44, 0.93	0.42, 0.82
	p value		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001		0.023	0.001		0.019	0.002
Rate of Exacerbations requiring Hospitalisation or ED visits	n	346	538	846	77	141	204	**Due to insufficient events in SIRIUS no analysis could be performed**			120	197	299	168	251	353	43	56	95	76	88	127
	Rate ratio		**0.53**	**0.60**		**0.32**	**0.33**					**0.38**	**0.37**		**0.37**	**0.37**		**0.54**	**0.44**		**0.55**	**0.47**
	95% CI		0.33, 0.84	0.40, 0.89		0.14, 0.73	0.16, 0.70					0.19, 0.74	0.21, 0.66		0.20, 0.69	0.21, 0.63		0.17, 1.68	0.16, 1.18		0.21, 1.45	0.19, 1.12
Comparison vs placebo	p value		0.007	0.012		0.007	0.004					0.004	<0.001		0.002	<0.001		0.284	0.102		0.227	0.088
Rate of Exacerbations requiring Hospitalisation	n	346	538	846	77	141	204	**Due to insufficient events in SIRIUS no analysis could be performed**			120	197	299	**Due to insufficient events in SIRIUS no analysis could be performed**			43	56	95	**Due to insufficient events in SIRIUS no analysis could be performed**		
	Rate ratio		0.50	0.49		**0.43**	**0.39**					**0.44**	**0.39**					**0.53**	**0.41**			
	95% CI		0.28, 0.89	0.30, 0.81		0.16, 1.12	0.16, 0.95					0.19, 1.02	0.19, 0.82					0.10, 2.75	0.10, 1.64			
Comparison vs placebo	p value		0.018	0.005		0.085	0.037					0.057	0.013					0.452	0.207			
SGRQ[3]	n	**No analysis possible as no SGRQ results in DREAM**			**No analysis possible as no SGRQ results in DREAM**			55	75	117	**No analysis possible as no SGRQ results in DREAM**			104	126	184	**No analysis possible as no SGRQ results in DREAM**			49	51	67
	Difference								**-10.9**	**-10.1**					**-8.0**	**-7.7**					**-4.3**	**-4.3**
Comparison vs placebo	95% CI								-17.0, -4.8	-15.7, -4.6					-12.0, -3.9	-11.4, -3.9					-9.6, 0.9	-9.3, 0.7
	p value								<0.001	<0.001					<0.001	<0.001					0.106	0.093
ACQ[4]	n	298	465	732	76	137	199	92	163	226	119	191	291	168	251	353	43	54	92	76	88	*127*
	Difference		**-0.34**	**-0.29**		**-0.76**	**-0.75**		**-0.78**	**-0.76**		**-0.56**	**-0.57**		**-0.58**	**-0.59**		**-0.30**	**-0.37**		**-0.43**	***-0.46***
Comparison vs placebo	95% CI		-0.48, -0.20	-0.42, -0.17		-1.05, -0.47	-1.03, -0.47		-1.05, -0.50	-1.03, -0.50		-0.79, -0.33	-0.79, -0.35		-0.79, -0.38	-0.78, -0.39		-0.71, 0.10	-0.73, 0.00		-0.75, -0.12	*-0.75, -0.16*
	p value		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001		0.144	0.050		**0.007**	***0.002***

1. In line with NICE methodological guidance, the meta-analysis was performed following the inverse variance method using estimates from each study (logarithm of rate ratio for exacerbations, difference from placebo for SGRQ and ACQ) along with their standard errors. 2. This is different from the meta-analyses presented in the Integrated Summary of Efficacy (ITT results above), which used a model including subjects from DREAM and MENSA an additional covariate for study. This was possible because both studies used similar covariates. Such a model including SIRIUS could not be performed as this study used different model covariates.
3. No SGRQ results were collected for DREAM therefore no DREAM + MENSA analysis was possible. Please note that for the same reason the DREAM, MENSA plus SIRIUS column is a meta-analysis of MENSA and SIRIUS only (SGRQ row only).
4. The initial ACQ model for SIRIUS did not converge as there were more subjects than time-points for analysis. We have therefore only included data from weeks 4, 8, 12, 16, 20, and 24 in this analysis in order to reach convergence.

A25. Section 4.9.3.1 of the company's submission. Please clarify whether the numbers, specifically the meta-analysis numbers, are correct throughout this section. For example:

a. Table 54, pg122-123. Mepolizumab 75mg IV has a rate ratio (RR) of 0.40 for DREAM and mepolizumab 75mg IV/100 mg subcutaneous has a RR of 0.52 for MENSA. The combined RR for these groups is given as 0.53. In Figure 17, pg. 114 the RR for this combined group is given as 0.46.

b. Table 55, mepolizumab 75mg IV has Rate Ratios of 0.61 for both DREAM and MENSA but a combined rate ratio of 0.57. Further, clarify why for mepolizumab 100mg subcutaneous is blank for DREAM & MENSA, rather than containing the MENSA results.

The reason for the apparent differences between rate ratios is due to the statistical methods employed for the meta-analysis.

For Tables 54 and 55, meta-analysis was performed on individual patient data. Covariate modelling was applied separately to each study and to the combined dataset. (Covariate adjustment for the meta-analysis included a covariate for study to allow for between-study differences). These covariates such as history of exacerbations affect the treatment estimates in the individual study analyses differently to the combined analysis. This explains why mepolizumab 75mg IV has a rate ratio (RR) of 0.40 for DREAM and mepolizumab 75mg IV/100 mg subcutaneous has a RR of 0.52 for MENSA while the combined RR for these groups is 0.53. This is also the explanation for why the rate ratios in table 55 are 0.61 for both DREAM and MENSA but a combined rate ratio of 0.57.

Results in Figure 17, page 114 were part of a different meta-analysis to tables 55 and 56. This meta-analysis uses a different approach, because some of the analyses for this meta-analysis included other studies as well as DREAM and MENSA. Individual patient data was not available for the Haldar study for example and different covariates were used in the analysis of SIRIUS to those in DREAM and MENSA. Meta-analysis of relative rates of exacerbations here was therefore performed using the inverse variance fixed effects method to combine estimated rate ratios and standard errors from each individual study.

For table 55, we agree it would have been possible to include the mepolizumab 100mg subcutaneous results for MENSA in the DREAM & MENSA part of the table. However, we wanted to make clear that the 100mg subcutaneous dose was included in MENSA only and not included in the DREAM study.

Whilst completing a thorough check of the data within this section, we have provided two updated tables, where minor numerical discrepancies were found in some of the figures, this has been highlighted within Table 25 and Table 26:

Table 25: Analysis of Rate of Clinically Significant Exacerbations (DREAM, MENSA and Meta-Analysis, ITT Population)

Rate of Clinically Significant Exacerbations	Placebo N=346	Mepolizumab 100 mg SC	Mepolizumab 75 mg IV	Mepolizumab 75 mg IV/	Mepolizumab All Doses5

		N=194	N=344	100 mg SC[4] N=538	N=846
DREAM					
n	155		153		461
Exacerbation rate/year	2.40		1.24		1.28
Comparison vs. placebo[1]					
Rate ratio (mepolizumab/placebo)	---		0.52		0.53
(95% CI)	---		(0.39, 0.69)		(0.43, 0.67)
p-value	---		<0.001		<0.001
MENSA					
n	191	194	191	385	385
Exacerbation rate/year	1.74	0.83	0.93	0.88	0.88
Comparison vs. placebo[2]					
Rate ratio (mepolizumab/placebo)	---	0.47	0.53	0.50	0.50
(95% CI)	---	(0.35, 0.64)	(0.40, 0.72)	(0.39, 0.65)	(0.39, 0.65)
p-value	---	<0.001	<0.001	<0.001	<0.001
DREAM & MENSA					
n	346		344	538	846
Exacerbation rate/year	1.91		1.00	0.98	1.00
Comparison vs. placebo[3]					
Rate ratio (mepolizumab/placebo)	---		0.52	0.51	0.52
(95% CI)	---		(0.42, 0.64)	(0.42, 0.62)	(0.44, 0.62)
p-value	---		<0.001	<0.001	<0.001

1. Analysis performed using a negative binomial regression model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable), and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. 2. Analysis model as in footnote [1]; estimates based on weighting applied to each level of class variable determined from observed proportions. 3. Analysis model as in footnote [2] where region is as defined for the meta-analysis and with an additional covariate of study. 4. For DREAM, the 75 mg IV/100 mg SC grouping is the same as the 75 mg IV grouping, since DREAM does not include a 100 mg SC dose. 5. DREAM includes 75, 250, and 750 mg IV. MENSA includes 75 mg IV and 100 mg SC; therefore, the All Doses grouping is the same as the 75 mg IV/100 mg SC grouping. DREAM+MENSA include 75, 250, and 750 mg IV and 100 mg SC.

Table 26: Analysis of Rate of Exacerbations Requiring Hospitalisation/ED Visits (DREAM, MENSA and Meta-Analysis, ITT Population)

Rate of Exacerbations Requiring Hospitalisation/ED Visits	Placebo N=346	Mepolizumab 100 mg SC N=194	Mepolizumab 75 mg IV N=344	Mepolizumab 75 mg IV/ 100 mg SC[4] N=538	Mepolizumab All Doses[5] N=846
DREAM					
n	155		153		461
Exacerbation	0.43		0.17		0.22

rate/year					
Comparison vs. placebo[1]					
Rate ratio (mepolizumab/placebo) (95% CI) p-value	---- ---- ----		0.40 (0.19, 0.81) 0.011		0.50 (0.29, 0.85) 0.011
MENSA					
n Exacerbation rate/year	191 0.20	194 0.08	191 0.14	385 0.11	385 0.11
Comparison vs. placebo[2]					
Rate ratio (mepolizumab/placebo) 95% CI p-value	---- ---- ----	0.39 (0.18, 0.83) 0.015	0.68 (0.33, 1.41) 0.299	0.52 (0.28, 0.96) 0.037	0.52 (0.28, 0.96) 0.037
DREAM & MENSA					
n Exacerbation rate/year	346 0.26		344 0.15	538 0.14	846 0.16
Comparison vs. placebo[3]					
Rate ratio (mepolizumab/placebo) (95% CI) p-value	---- ---- ----		0.58 (0.35, 0.97) 0.037	0.53 (0.33, 0.84) 0.007	0.60 (0.40, 0.89) 0.012

1. Analysis performed using a negative binomial regression model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable), and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. 2. Analysis model as in footnote [1]; estimates based on weighting applied to each level of class variable determined from observed proportions. 3. Analysis model as in footnote [2] where region is as defined for the meta-analysis and with an additional covariate of study. 4. For DREAM, the 75 mg IV/100 mg SC grouping is the same as the 75 mg IV grouping, since DREAM does not include a 100 mg SC dose.
5. DREAM includes 75, 250, and 750 mg IV. MENSA includes 75 mg IV and 100 mg SC; therefore, the All Doses grouping is the same as the 75 mg IV/100 mg SC grouping. DREAM+MENSA include 75, 250, and 750 mg IV and 100 mg SC.

Network meta-analysis

A26. Please clarify what the inclusion/exclusion criteria were for the network meta-analysis, presented in a table using the PICOS format. Please include a rationale for the criteria used.

The inclusion and exclusion criteria applied for the network meta-analysis (NMA) is provided below in Table 27 in the requested PICOS format.

Table 27: PICOS, inclusion and exclusion criteria of the NMA

	Inclusion Criteria	Exclusion Criteria	Rationale
Population	**Disease and prior treatment criteria:**		The licence for mepolizumab had not been issued at

	Severe asthma patients aged ≥12 years receiving ≥ 1,000 µg/day BDP-equivalent ICS plus ≥ 1 additional controller and with a documented history (see below) of exacerbations. **Exacerbation history and treatment eligibility criteria differs by population specification:** ***Population 1: 'Overlap'*** Required exacerbation history: ≥ 2 SCS-treated exacerbation OR ≥ 1 severe exacerbation resulting in hospitalisation in previous 12 months. *Mepolizumab eligibility:* Mepolizumab RCTs - Based on expected licence (MENSA) Omalizumab RCTs – meeting disease criteria (background medication and exacerbation history). *Omalizumab eligibility:* Mepolizumab RCTs – Required based on EU omalizumab licence (weight, IgE and positive RAST test) Omalizumab RCTs – must include EU licence population. ***Population 2: 'Expanded overlap'*** Required exacerbation history: ≥ 1 exacerbation in the previous 12 months (defined as	• Mild and moderate asthma patients i.e those receiving ≤1000µg/day (BDP equivalent) ICS and no additional controller medication.	the time at which the NMA was conducted. The expected mepolizumab licence used in this NMA aligned to the inclusion criteria of MENSA. • Population 1 is a reasonable approximation of the overlap using IPD for mepolizumab to identify omalizumab eligible patients. • Population 2elaxes the exacerbation history to expand the dataset included for omalizumab.

	treatment with SCS or asthma hospitalisation or asthma ED visit) *Mepolizumab eligibility:* Mepolizumab RCTs – As per Population 1 'Overlap' Omalizumab RCTs – meeting disease criteria (background medication and less strict exacerbation history). *Omalizumab eligibility:* Mepolizumab RCTs – As per Population 1 'Overlap' Omalizumab RCTs – As per Population 1 'Overlap' ***Population 3: 'Full trial' [implemented in the economic model]*** Required exacerbation history: ≥ 1 exacerbation in the previous 12 months (defined as treatment with SCS or asthma hospitalisation or asthma ED visit) [as per Population 2: Expanded overlap] *Mepolizumab eligibility:* Mepolizumab RCTs – As per Population 1 'Overlap' Omalizumab RCTs – not required. *Omalizumab eligibility:* Mepolizumab RCTs – Not required Omalizumab RCTs – As per Population 1		• Population 3 incorporates all patients from the NMA eligible mepolizumab RCTs regardless of omalizumab eligibility.

	'Overlap'		
Intervention	*Core analyses*: Mepolizumab 100mg SC (expected EU licence at the time of study, inclusion criteria of MENSA) and omalizumab (EU licence) *Sensitivity analyses:* As above and mepolizumab 75mg IV	• Mepolizumab: Those not meeting the expected EU licence at time of study (MENSA inclusion criteria). • Omalizumab: Those not fulfilling the EU licence criteria.	• Identified by the NICE scope and BTS/SIGN guidelines.
Comparators	SoC (receiving ≥ 1,000 µg/day BDP-equivalent ICS plus ≥ 1 additional controller).	• Those receiving <1,000 µg/day BDP-equivalent ICS and no additional controller.	• Identified by the NICE scope and BTS/SIGN guidelines.
Outcomes	Pre-specified NMA end points (following a feasibility assessment). **Primary end points:** *Exacerbations* • Annualised rate of exacerbations, defined as requiring SCS (or at least a doubling of existing dose for maintenance OCS patients) and/or hospitalisation and/or emergency room treatment • Annualised rate of exacerbations, defined as requiring hospitalisation **Secondary end points:** • Change from baseline in % predicted FEV_1	• No pre-defined relevant and comparable efficacy or safety endpoints can be determined, extracted or calculated from the available RCT data	• End point was considered feasible and included in the NMA only if analysis of the end point was possible (i.e. data were available)
Study design	*Core analyses:* • Parallel-group RCTs of ≥12 weeks duration • Double blind study	• Other study types, such as: single-arm clinical trials; pre-clinical studies; Phase 1 studies; prognostic studies; retrospective studies; observational studies; case reports; cohort studies;	

		commentaries and letters that do not report RCTs; consensus reports; non-randomised clinical trials; reviews; meta-analyses (RCTs contributing to meta-analyses were retrieved) • Duration of follow-up < 12 weeks • Data from periods following protocol-driven change in ICS/OCS maintenance dosage	• Considered an insufficient exposure length to perform valid evaluations of the selected efficacy endpoints • Limit uncertainty in the resultant comparative efficacy.
	Sensitivity analysis • Open-label studies		

Additional clarification questions from the ERG

a. The GSK proposed population is defined as: "Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or dependency on systemic corticosteroids (mOCS)". Please clarify how "exacerbations" are defined in the proposed population.

An 'exacerbation' in the previous year (baseline) was defined in the clinical trial protocol as: '...asthma exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to Visit 1, despite the use of high-dose ICS. For subjects receiving maintenance CS, the CS treatment for the exacerbations must have been a two-fold increase or greater than their maintenance dose.'
This is aligned with the definition of the primary endpoint: '...clinically significant exacerbations of asthma as defined by worsening of asthma which required use of systemic corticosteroids and/or hospitalisation and/or Emergency Department (ED) visits. Use of systemic corticosteroids was defined as IV or oral steroid (e.g., prednisone) for at least 3 days or a single IM dose. For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days was required.'

These definitions were consistent throughout the phase IIb/III clinical trial programme and aligns with how "exacerbations" are defined in the proposed population.

b. Please clarify how "previous exacerbations" are defined in the subgroup analyses of MENSA (Table 22) and DREAM (Figure 14).

"Previous exacerbations" refers to the baseline exacerbations rate subjects experience in the previous year before entering the trial and the definition of exacerbation for MENSA is provided in answer (a) above. This was the same definition as in DREAM, which defined exacerbation as: '...asthma exacerbations requiring treatment with oral or systemic corticosteroids in the 12 months prior to Visit 1, despite the use of high-dose ICS and additional controller medication. For subjects receiving maintenance OCS with high-dose ICS plus controller, the OCS treatment for exacerbations had to be a two-fold or greater increase in the dose of OCS.'

Section B: Clarification on cost-effectiveness data

Please note that all of the ICERs reported below are with PAS ICERs.

B1. Priority Question: Please provide an individual ICER for the group of patients that constitute the additional patients in the company's proposed population. That is, "Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/μL at initiation of treatment and dependency on systemic corticosteroids with <4 exacerbations in the previous year". At present this ICER is obscured by the aggregation of the two populations.

The following model inputs were implemented as an additional subgroup population (> = 0.15 EOS + <4 Exacerbations + OCS) (please see Table 28).

Table 28: Model inputs for additional subgroup population (≥0.15 EOS + <4 exacerbations + OCS)

75mg IV + 100mg SC	≥0.15 EOS + <4 Exacerbations + OCS		
	pre-continuation (mepo)	SoC	Post-continuation (mepo)
N	41	33	
Exacerbation rate (Annualised)	1.02 (0.228)	1.40 (0.284)	0.38 (0.604)
Utility (SGRQ)	0.738 (0.032)	0.762 (0.042)	0.766 (0.033)
Exacerbations requiring OCS	37 (84.1%)		
Exacerbations requiring ED	4 (9.1%)		
Exacerbations requiring Hosp	3 (6.8%)		

Compared with the proposed population, people in this subgroup have a lower exacerbation rate in each of the model states: 1.02, rather than 1.206 in pre-continuation (mepo), 1.40 rather than 2.650 in SoC, and 0.38 compared with 0.645 in post continuation (mepo). Utilities, however are lower for the pre and post continuation (mepo) states, than in the proposed population, 0.738 rather than 0.777 in pre-continuation, and 0.766 rather than 0.795 in post continuation, but considerably higher in SoC state (0.762 compared with 0.708), this may be explained by the fact that all of this subgroup would be taking OCS and so there is a protective effect on day-to-day asthma symptoms.

Table 29: Model results for additional subgroup population (≥0.15 EOS + <4 exacerbations + OCS)

	Total Cost	Δ Cost	Total QALY	Δ QALY	ICER (vs.)
Mepolizumab + SoC	[redacted]	-	[redacted]		
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	£78,716

The resulting ICER in this subgroup is £78,716 as seen in Table 29. This is primarily attributed to the incremental QALYs, which are [redacted] rather than [redacted] in the proposed population.

This difference in incremental QALYs, is in part due to low absolute exacerbation rates observed in his subgroup, as well as proportionally fewer more severe exacerbations: the breakdown in the proposed population was 78% requiring OCS use, 11% requiring an emergency room visit and 11% requiring hospitalisation, compared with 84%, 9% and 7% in this subgroup, for exacerbations requiring OCS, ED and hospitalisation, respectively, which could potentially be attributed to these people's asthma being controlled by the OCS. This in turn leads to small differences in asthma related mortality, and the lower differences observed in utility values between mepolizumab and SoC. Additionally, there is uncertainty in these values, due to the small numbers of patients in this subgroup population (n=74).

In this subgroup, maintenance OCS use may be controlling asthma and thus the number and severity of exacerbations experienced. However this may be at the expense of being on maintenance OCS and on the impact that might have on the person's health in the longer term. For these patients, a treatment objective is to reduce dependence on oral corticosteroids whilst maintaining asthma control and in the modelling, this results in a higher ICER, potentially reflecting the challenges of capturing the benefit of OCS reduction.

However whilst considering this population on its own, it would appear to provide a less cost effective use of NHS resources, we believe that to restrict a recommendation by excluding this subgroup would be inequitable to these patients. These patients are more severe (at Step 5 in the BTS guidelines). If any resulting NICE guidance excluded this population the only potential option for these patients to have access to mepolizumab would be to withdraw OCS therapy and then if they began to exacerbate further, they would potentially become eligible for treatment as part of our Step 4 proposed population. As we are concerned about the impact of such an outcome on patients, we have provided mepolizumab at a price where, in considering the totality of the proposed population, which includes this subgroup, the ICER lies under the cost effectiveness threshold.

B2. Priority Question. Please provide an analysis of patients in the SIRIUS ITT population and estimate the threshold level of QALYs that would be required from reduced oral corticosteroid use for the ICER to be £20,000 per QALY and £30,000 per QALY.

It was not possible to obtain a re-analysis to obtain all of the necessary model inputs from SIRIUS in the time given, however utility values were obtained, and the model was re-run using these values (overwritten on the sheets with utility values in column X- AA) (please see Table 30).

Table 30: Model inputs in SIRIUS ITT population, utility data

SIRIUS	Utility SGRQ		
	pre-continuation (mepo)	pre-continuation (SoC)	Post-continuation (mepo)
ITT population	0.710 (0.027)	0.706 (0.026)	0.716 (0.029)

Furthermore, the OCS module is switched to 'Yes' (median dose reduction) for completeness (however this attributes an [redacted] QALYs only) and the proportion of patients on OCS is set to 100% (aligned with SIRIUS population).

Table 31: SIRIUS ITT population

	Total Cost	Δ Cost	Total QALY	Δ QALY	ICER (vs.)
Mepolizumab + SoC	[redacted]	[redacted]	[redacted]		
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	£51,289

Using the utility data from SIRIUS in the ITT population, would give an ICER of £51,289 (please see Table 31).

Please note that the incremental QALYs observed in the modelling in the ITT population in the base case was [redacted] compared with [redacted] in this analysis. It is worth bearing in mind that the aim of SIRIUS was to reduce OCS burden, whilst maintaining asthma control through the use of mepolizumab. Because of this, the reduction in exacerbations was not as much as in MENSA and therefore, we wouldn't expect to see as much of an improvement in QALYs as was seen in MENSA, because the effect of taking away OCS masks the true effect on the QALYs: should it be required that OCS be stopped prior to permitting commencement with mepolizumab, then it is anticipated that the baseline event rate would be higher, and thus the amount of HRQoL benefit that could be achieved would be greater. However, we consider that such a decision would be unethical. Note that, introducing mepolizumab with OCS dependence, gave an odds ratio in SIRIUS for the ITT population of 2.39 for achieving a reduction in OCS compared with SoC, whilst obtaining a reduction in exacerbation rate (RR=0.68) and whilst improving asthma control (-0.52 (MCID is 0.5)).

In answer to the second part of this question, in order to have an ICER of £30,000 for this population, the total QALYs gained for mepolizumab vs. SoC would need to be [redacted], compared with the [redacted] seen in Table 31. Thus, the contribution from reduced oral corticosteroid use would need to be [redacted].

In order to have an ICER of £20,000 for this population, the total QALYs for mepolizumab vs. SoC would need to be [redacted], compared with the [redacted] seen in Table 31. Thus, the contribution from reduced oral corticosteroid use would need to be [redacted].

B3. Priority Question. Please clarify the ICER for mepolizumab using only the data from the 100mg subcutaneous groups.

As described in Section 4.7.3.2 of the main submission, bioequivalence was deemed between 75mg IV and 100mg SC and hence the data were pooled in order to increase the

certainty in the results. In the time available it has not been possible for all of the values to be obtained in order to recalculate the ICER, however exacerbation rates have been obtained, and the SGRQ values for the 75mg IV and 100mg SC data have already been presented in the main submission, and provide some information on what we might expect to see from such an analysis. Thus, the following information may give some clarity on this question to the ERG:

The model inputs for exacerbation rates, if only mepolizumab 100mg SC is used, are provided below (Table 32), adjacent to the base case model inputs based on 75mg IV + 100mg SC.

Table 32: Exacerbation rates comparing 75mg IV + 100mg SC with 100mg SC derived rates

	Base case model (75mg IV + 100mg SC)			Implementing only 100mg SC		
	ITT	GSK proposed population excluding OCS with <4 exacerbations	GSK proposed population	ITT	GSK proposed population excluding OCS with <4 exacerbations	GSK proposed population
Exacerbation rate (Annualised)						
pre-continuation (mepo) (SE)	0.877 (0.085)	1.213 (0.148)	1.206 (0.127)	0.83 (0.120)	1.22 (0.203)	1.32 (0.169)
pre-continuation (SoC) (SE)	1.744 (0.098)	3.101 (0.179)	2.65 (0.157)	NA	NA	NA
Post-continuation (mepo) (SE)	0.55 (0.146)	0.723 (0.232)	0.645 (0.224)	0.53 (0.207)	0.79 (0.298)	0.62 (0.309)

If only 100mg SC mepolizumab data are used, as shown in Table 32, the exacerbation rates do not vary considerably across the populations and there is no trend in either direction in the difference in exacerbation rates. As expected the SE are wider when the 75 mg IV data is excluded.

Data on SGRQ for 75mg IV and 100mg SC are presented in the main submission, in section 4.7.4.3 Table 26, (reproduced in Table 33 below). SGRQ is mapped to EQ-5D utility for the modelling, thus the trends observed in these data are expected to be those in the mapped EQ-5D utility values. The SGRQ values (change from baseline) presented, show that the difference (absolute improvement) versus placebo is greater for 100mg SC mepolizumab arm compared with the 75mg IV mepolizumab arm and this remains true across all populations (please see Table 33). Therefore it can be speculated with some degree of reassurance that pooling the IV and SC arms takes a more conservative approach to modelling day-to-day symptoms and if only the SC arm was to be modelled this would likely further improve the ICER for all populations considered.

Table 33: Analysis of Change from Baseline in St. George's Respiratory Questionnaire (SGRQ) Score (ITT, GSK proposed population and GSK proposed population excluding OCS users with <4 exacerbations) [data taken from main submission, Section 4.7.4.3 Table 26]

MENSA	ITT	GSK proposed population excluding mOCS users with <4 exacerbations[1]	GSK proposed population[2]

SGRQ	Placebo N=191	Mepo 100mg SC N=54	Mepo 75mg IV N=48	Placebo N=45	Mepo 100mg SC N=54	Mepo 75mg IV N=48	Placebo N=64	Mepo 100mg SC N=78	Mepo 75mg IV N=65
n[1]	177	184	174	40	53	42	59	75	58
LS Mean (SE)	37.7 (1.16)	30.7 (1.13)	31.2 (1.16)	42.4 (2.64)	29.5 (2.32)	32.5 (2.59)	41.3 (2.08)	31.3 (1.86)	33.4 (2.12)
LS Mean Change (SE)	-9.0 (1.16)	-16.0 (1.13)	-15.4 (1.16)	-8.2 (2.64)	-21.1 (2.32)	-18.1 (2.59)	-8.7 (2.08)	-18.7 (1.86)	-16.6 (2.12)
Comparison vs. Placebo									
Diff	---	**-7.0**	**-6.4**	---	**-12.8**	**-9.9**	---	**-10.00**	**-7.90**
(95% CI)	---	**(-10.2, -3.8)**	**(-9.7, -3.2)**	---	**(-19.9,-5.8)**	**(-17.2,-2.5)**	---	**(-15.5,-4.5)**	**(-13.8,-2.0)**
p-value	---	**<0.001**	**<0.001**	---	**<0.001**	**0.009**	---	**<0.001**	**0.008**

[1]Note: Only subjects with a Baseline and Week 32 assessment are included in the analysis. Note: Analysis performed using analysis of covariance with covariates of baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), baseline % predicted FEV_1, and treatment. [2]Note: Only subjects with a Baseline and Week 32 assessment are included in the analysis. Note: Analysis performed using analysis of covariance with covariates of baseline, region, baseline % predicted FEV_1, and treatment.

B4. Priority Question. Please clarify why the exacerbation rates from COLUMBA and COSMOS were not used for the long-term extrapolation data for mepolizumab. Please provide an analysis assessing the impact on the ICER of using these values.

COLUMBA is an ongoing OLE study (Extension to DREAM) and therefore only interim analyses were included in the clinical effectiveness section of the submission. Data on the OLE study COSMOS (extension study to MENSA and SIRIUS) were not included because at the time of the submission, preparation of the clinical study report had not been completed early enough for inclusion.

Due to the extent of the requested analyses and limited available time, we have not been able to answer fully this question, however we believe the following goes someway to providing a response. Since COLUMBA has yet to complete, we focus on COSMOS.

COSMOS is a long term safety study with the primary objective to capture the frequency of AEs. Patients already on mepolizumab coming into the study (from either MENSA or SIRIUS) remained on treatment, while patients previously receiving placebo, open label treatment with 100mg SC mepolizumab was initiated at 4-weekly intervals. As part of the secondary/tertiary outcomes, the rate of annualised exacerbations was captured.

In COSMOS, at the end of 52 weeks, the estimated annualised rate of exacerbations was 0.93 (0.83, 1.04) across the whole study population and the annualised rate of exacerbations for patients previously treated with mepolizumab was 0.90 (0.78, 1.04). This is reasonably comparable to the annualised exacerbation rate reported for subjects on mepolizumab in the 32 week MENSA study for the ITT population (75mg IV 0.98, 100mg SC 0.74).

Whilst a formal analysis assessing the impact of the ICER has not been conducted, comparing the exacerbation rates of subjects from the ITT population on mepolizumab from COSMOS compared to MENSA, suggests that any impact on the resultant ICER is likely to be small. This conclusion makes the assumption that this trend is true in the GSK proposed populations for which these analyses have not been conducted.

B5. Priority Question. Please clarify how the annual exacerbation rate is calculated for those meeting mepolizumab's continuation criteria. The assumed number (0.645, Transitions!AD17 in the model) for those meeting the criteria in the company's proposed population is markedly lower than that for all patients in this population (1.206, Transitions!AD14 in the model) despite 92.3% of the patients meeting the criteria.

Because the SmPC for mepolizumab states that:

'the need for continued therapy should be considered at least on an annual basis'

for the purposes of the model, for those being treated with mepolizumab, the criteria for meeting the continuation review and continue on mepolizumab were those patients who experience:

1. no change in annualised exacerbation rate or
2. an improvement over baseline rates

This review occurred at 32 weeks, at the end of the MENSA trial, and in lieu of 12 month data, an assumption was made that the 32 week data would be equivalent to 12 months data. The annual exacerbation rate in subjects continuing treatment with mepolizumab was calculated using data from Week 16 to end of study (Week 32) in MENSA (using a negative binomial model). However, the proportions continuing treatment were defined at end of study (week 32) as this was the closest time-point to the time at which the criteria is to be applied.

Only patients who experienced an increase in annualised exacerbation rate from that observed at baseline were discontinued from mepolizumab. The proportion of patients assumed to continue on mepolizumab therapy (derived from people in MENSA meeting the criteria for the sub-population) was 92.3%, thus 7.7% did not meet the continuation criteria.

The SAS outputs have been re-reviewed and checked. No errors have been identified in the analysis (please see Table 34). As previously mentioned, the data on exacerbation rates used within the state: 'people on treatment' over the first 12 months, were taken from MENSA for those in the mepolizumab treatment arm. Thus, they combine those people who respond as well as those who do not respond to treatment, as would be seen in clinical practice, prior to a continuation review. Thus, the continuation assessment allows those people who do not respond to treatment to stop taking treatment, and the resulting exacerbation rate for those who do respond, illustrates the efficacy of mepolizumab in those patients who do respond to treatment.

Table 34: Annual exacerbation rates, within the GSK proposed population

	N	Annualised exacerbation rate	SE
Exacerbation rate pre-continuation [mepolizumab]*	143	1.21	0.127
Exacerbation rate pre-continuation [SoC]*	64	2.65	0.157
Exacerbation rate post – continuation [mepolizumab]	115	0.64	0.224

*Annualised exacerbation rate, week 32, from baseline.

B6. Priority Question. Please provide an analysis assessing the impact on the ICER using the meta-analysis of MENSA and DREAM on the company's proposed population and the company's proposed population excluding mOCS users.

As part of the meta-analysis, the combined data from MENSA and DREAM were used to obtain exacerbation rates (please see Table 35). Two different analyses were run: the first using the SGRQ mapped data to EQ-5 D utility and the second, using EQ-5 D elicited from DREAM. The other model inputs were the same as for the base case.

Table 35: Exacerbation rates for DREAM and MENSA combined

	GSK proposed population excluding OCS with <4 exacerbations	GSK proposed population
Exacerbation rate (Annualised)		
pre-continuation (mepo)	1.117	1.139
pre-continuation (SoC)	3.318	2.775

The exacerbation rates for mepolizumab are slightly lower than in the base case analysis, and for SoC they are slightly higher. This leads to ICERs that are slightly improved, compared with the base case analysis of £19,526 (using SGRQ mapped to EQ-5D) as seen in Table 36. Using the EQ-5D from DREAM the ICER is marginally higher.

Table 36 ICERs from the meta-analysis of MENSA and DREAM

	GSK proposed population excluding mOCS users with <4 exacerbations					GSK proposed population				
	Total cost	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**	**Total cost**	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**
SGRQ mapped (MENSA)										
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£14,679	[redacted]	[redacted]	[redacted]	[redacted]	£18,779
EQ-5D (DREAM)										
Mepo + SoC	[redacted]		[redacted]	[redacted]		[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£17,269	[redacted]	[redacted]	[redacted]	[redacted]	£19,932

B7. Priority Question. Please clarify whether the continuation rule assumed in the model (that is, patients continue unless they worsen) has been proposed elsewhere (e.g. guidelines). If possible, provide exploratory analyses to assess the impact on the ICER of varying the continuation rule, that is assuming patients had to have improved by a certain amount (as gauged by reduction of exacerbations or OCS use).

The continuation rule is included in the SmPC for mepolizumab, which states:

'the need for continued therapy should be considered at least on an annual basis as determined by physician assessment on the patient's disease severity and level of control of exacerbations'.

As far as we know, this continuation rule has not been proposed elsewhere, for example in guidelines or other published documents. However, from clinical feedback it is clear that in practice patients will be assessed as part of their routine follow-up to ensure only those who continue to benefit from treatment remain on treatment. This is true of other biologics not only in this therapy area (i.e. omalizumab) but also other therapy areas where biologics are in use.

Exacerbation reduction is a key treatment objective for mepolizumab, and as exacerbations are relatively infrequent events, and to avoid seasonal variability, an annual assessment was considered clinically relevant for mepolizumab. Patients with severe asthma who experience frequent exacerbations generally maintain a pattern of frequent exacerbations over time, and therefore one year is considered to be an appropriate period for the assessment of exacerbation reduction.

The continuation rule applied in the model is that only those patients that see a worsening in exacerbation frequency from baseline are discontinued on mepolizumab, and receive SoC alone with its associated costs and outcomes. This continuation review is a pragmatic approach and takes into consideration those patients at Step 5 on maintenance OCS, who may be less likely to experience a further reduction in exacerbations given their maintenance

OCS therapy. However in these instances mepolizumab provides the opportunity to reduce OCS exposure and therefore the longer term risks associated with OCS whilst maintaining asthma control. For this reason, in the economic model we do not believe it is appropriate to quantify the level of improvement, in this instance in terms of quantifying those who achieve no, versus a reduction in e.g. 1 or 2 etc exacerbations; clinically these severe asthma patients could present differently.

A number of measures were also previously assessed, to investigate whether there was an alternative/additional short-term measure that could reliably and robustly predict future exacerbation reduction and hence identify a continuation rule at an earlier time point. These measures included the asthma control questionnaire (ACQ), change from baseline FEV_1, eosinophil reduction and physician-rated response. Various time points were considered including an assessment at 16 weeks. Despite this effort, no short-term measure was identified that could robustly predict non-response to mepolizumab in terms of exacerbation reduction.

Therefore, although in clinical practice the clinician treating the patient may make a more holistic assessment as to whether the patient is deemed to respond, we would recommend at the very least a review of exacerbation frequency at 12 months as per the SmPC.

Additional scenario analyses were performed where the ICER is re-calculated for the three populations applying one of the following:

1. Exploring the impact of 100%, 90%, 80% and 50% continuing by the end of year one.
2. Exploring the impact of applying the continuation criteria at 6m and 9m (not the 12 m as per the base case)
3. Exploring the impact of varying the % continuing (100%, 80% and 50%) where the continuation criteria is applied at 6m
4. Exploring the impact of varying the % continuing (100%, 80% and 50%) where the continuation criteria is applied at 9m

As shown in the results overleaf (please see Table 37), the ICERs remain relatively stable across all of these scenario analyses. The cost-effectiveness of mepolizumab reduces as the proportion of patients who discontinue increases mainly driven by the reduction in the overall incremental QALYs. The cost-effectiveness of mepolizumab improves the sooner the continuation criteria are applied since this consequently means the application of the post continuation exacerbation rates and day-to-day utility takes place sooner. Overlaying a smaller proportion of patients who continue where continuation is applied earlier has limited impact on the overall ICER, which remains true across all populations.

Table 37: Resultant ICERs based on changing the % meeting the continuation criteria and the time at which the continuation criteria is applied

	ITT					GSK proposed population excluding mOCS users with <4 exacerbations					GSK proposed population				
	Total cost	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**	**Total cost**	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**	**Total cost**	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**
Base case															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£31,659	[redacted]	[redacted]	[redacted]	[redacted]	£15,394	[redacted]	[redacted]	[redacted]	[redacted]	£19,526
Assume 100% continue after year 1															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£31,557	[redacted]	[redacted]	[redacted]	[redacted]	£15,382	[redacted]	[redacted]	[redacted]	[redacted]	£19,463
Assume 90% continue after year 1															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£31,670	[redacted]	[redacted]	[redacted]	[redacted]	£15,425	[redacted]	[redacted]	[redacted]	[redacted]	£19,547
Assume 80% continue after year 1															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£31,807	[redacted]	[redacted]	[redacted]	[redacted]	£15,477	[redacted]	[redacted]	[redacted]	[redacted]	£19,648
Assume 50% continue after year 1															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£32,465	[redacted]	[redacted]	[redacted]	[redacted]	£15,725	[redacted]	[redacted]	[redacted]	[redacted]	£20,136
Continuation criteria is applied at 6 months															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£30,929	[redacted]	[redacted]	[redacted]	[redacted]	£15,135	[redacted]	[redacted]	[redacted]	[redacted]	£19,002
Continuation criteria is applied at 9 months															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£31,241	[redacted]	[redacted]	[redacted]	[redacted]	£15,246	[redacted]	[redacted]	[redacted]	[redacted]	£19,226
Assume 90% continue, continuation criteria applied at 6m															

Mepo + SoC	[redacted]														
SoC	[redacted]				£30,935	[redacted]				£15,153	[redacted]				£19,014
Assume 80% continue, continuation criteria applied at 6m															
Mepo + SoC	[redacted]														
SoC	[redacted]				£31,012	[redacted]				£15,184	[redacted]				£19,070
Assume 50% continue, continuation criteria applied at 6m															
Mepo + SoC	[redacted]														
SoC	[redacted]				£31,409	[redacted]				£15,340	[redacted]				£19,357
Assume 90% continue, continuation criteria applied at 9m															
Mepo + SoC	[redacted]														
SoC	[redacted]				£31,250	[redacted]				£15,270	[redacted]				£19,242
Assume 80% continue, continuation criteria applied at 9m															
Mepo + SoC	[redacted]														
SoC	[redacted]				£31,355	[redacted]				£15,311	[redacted]				£19,318
Assume 50% continue, continuation criteria applied at 9m															
Mepo + SoC	[redacted]														
SoC	[redacted]				£31,876	[redacted]				£15,511	[redacted]				£19,700

B8. If possible, please provide the ICERs that would be generated using the populations requested in question A9.

A9 is a request for tables of clinical outcome data (including clinically significant exacerbations, hospitalisations and QoL) for each study with the original ITT populations and the two company proposed populations side by side.

Information on exacerbation rates were obtained from DREAM (please see Table 38), alongside data previously presented on EQ-5D values from DREAM (table 129 of the main submission) were used for the requested analysis.

Table 38. Model inputs for exacerbation rates, from DREAM

75mg IV	DREAM		
	pre-continuation (mepo)	pre-continuation (SoC)	Post-continuation (mepo)
ITT population			
N	153		133
Exacerbation rate (Annualised)	1.04 (0.112)	2.02 (0.197)	0.83 (0.141)
≥0.15 & ≥4 Exacerbations			
N	39		37
Exacerbation rate (Annualised)	1.18 (0.204)	3.81 (0.177)	1.05 (0.138)*
GSK proposed population			
N	54		50
Exacerbation rate (Annualised)	1.21 (0.168)	3.33 (0.136)	0.73 (0.236)
* Only available for all mepo doses, not for 75mg alone			

It was not possible to obtain a re-analysis to obtain all of the necessary model inputs from SIRIUS in the time given, however utility values were obtained, and so the ICERs for SIRIUS were obtained using base case model inputs, with the SIRIUS utility values (please see Table 39).

Table 39. Model inputs from SIRIUS

SIRIUS	Utility (SGRQ)		
	pre-continuation (mepo)	pre-continuation (SoC)	Post-continuation (mepo)
ITT population	0.710 (0.027)	0.706 (0.026)	0.716 (0.029)
GSK proposed population	0.711 (0.028)	0.718 (0.029)	0.696 (0.036))

Note, it is not possible to present data for the ≥0.15 & ≥4 exacerbation population, because of the nature of the trial, in that all people were on OCS, and so this population is the proposed population.

In the ITT population, these results show a smaller improvement pre and post continuation than in proposed population in MENSA, whilst the subgroup population shows a decline in utility pre and post continuation. Given the small number of patients in whom utility data were utilised (n=132 across the three groups), any results from this analysis should be interpreted with caution.

Table 40: ICERs by mepolizumab trial

	ITT					GSK proposed population excluding mOCS users with <4 exacerbations					GSK proposed population				
	Total cost	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**	**Total cost**	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**	**Total cost**	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**
MENSA															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£31,659	[redacted]	[redacted]	[redacted]	[redacted]	£15,394	[redacted]	[redacted]	[redacted]	[redacted]	£19,526
DREAM															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£40,886	[redacted]	[redacted]	[redacted]	[redacted]	£16,907	[redacted]	[redacted]	[redacted]	[redacted]	£17,630
SIRIUS															
Mepo + SoC	[redacted]		[redacted]			N/A		N/A			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£51,717	N/A	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	[redacted]	£32,374

The corresponding ICERs are shown in Table 40. The ICERs from MENSA were already available, and the ICERs for DREAM and SIRIUS, obtained using the additional information, as described above.

In the SIRIUS analysis, the incremental QALYs are lower compared than from MENSA, due to the lower differences observed in the utility values between mepolizumab and SoC in SIRIUS. For example, in SIRIUS (MENSA), the pre continuation utility value used was 0.710 (0.777), post continuation, was 0.716 (0.795) and SoC, 0.706 (0.708). As previously explained in B2, the aim of SIRIUS was on reducing OCS dependence and therefore, one wouldn't expect to see as much of an improvement in QALYs as was seen in MENSA, because the effect of taking away OCS masks the true effect on the QALYs. Thus the use of QALY data from SIRIUS is expected to underestimate the true impact of mepolizumab.

Please note that the values presented in B2 and B8 differ slightly because for B2 the OCS module was turned on, whereas in B8 it was turned off.

B9. Please clarify how mapping from the SGRQ to the EQ-5D would resolve the fundamental problems of using the EQ-5D in asthma that were stated by the company in section 5.4.1 of the submission.

It is a fair reflection that the mapping of SGRQ to EQ-5D would not resolve the issues identified with using the EQ-5D in a severe asthma population.

Nevertheless, SGRQ was collected in the phase III programme, and EQ-5D was only collected as part of the phase II programme, thus in order to obtain utilities from the phase III trial it was necessary to do so through the use of a mapping algorithm. The selected algorithm by Starkie et al, has demonstrated predictive ability between the SGRQ and the EQ-5D: the results of a validation exercise of the mapping algorithm showed that the algorithm could predict EQ-5D scores from SGRQ derived values.

Methodologically it did not seem appropriate to implement the directly elicited EQ-5D data from the phase II DREAM patient population since one third of patients reported perfect health at baseline which would suggest that in this severe asthma population, EQ-5D was not a sensitive instrument to measure HRQL and hence its exclusion from the Phase III MENSA trial. Clinicians confirmed that this result does not reflect the severe asthma patients they see in clinic (please refer to the discussion in the main submission page 178, Quality of Life Measure). However, as we collected SGRQ in MENSA which did not show the same ceiling effects as that seen with EQ-5D it seemed more akin to clinical practice and in an attempt to generate ICER's for the committee to consider to map these values to EQ-5D and implement these values in the model. Our conclusion here being that mapping SGRQ values (a valid respiratory HRQL instrument) to EQ-5D is still likely to result in more sensitive or at least reflective EQ-5D values than those directly elicited.

Finally, recognising NICE's preference for directly elicited EQ-5D derived utility, when implemented in the model as a scenario analyses (see Table 147 of the main submission page 246) the resultant ICER for the GSK proposed population (£20,863/QALY gained) still remains within an acceptable cost-effectiveness threshold.

B10. If possible, please clarify how the answer to A12 would qualitatively affect the ICER.

As described in response to A12, when comparing across all three trials (DREAM, MENSA and SIRIUS), infections was the most common adverse event of special interest, followed by systemic/local site reactions. However, when comparing placebo with the mepolizumab arms, the number of infections occurring was relatively similar. There were some differences in the occurrence of systemic/local site reactions. In the integrated safety summary the incidence of injection site reactions with mepolizumab 100mg SC and placebo was 8% and 3% respectively, although we acknowledge that in clinical practice the SoC patients would not receive placebo injections and therefore would not have any injection site reactions.

The symptoms of an injection site reaction include stinging, erythema, itching, pain, swelling, warm to touch, ache, numbness, bruise, and induration. A quick search through the literature (non-targeted, non-systematic) identified a study exploring utilities and disutilities for attributes of injectable treatments for Type 2 diabetes where patients in Scotland completed standard gamble (SG) interviews to assess the utility of hypothetical health states and their own current health state (Boye etal., 2011). The disutility associated with an injection site reaction from a once per week injectable (0.873) compared to no injection site reaction

(0.882) was -0.010 (SE 0.151). Whilst this may overestimate the disutility associated with an injection site reaction as a result of being on a once monthly treatment with mepolizumab it does at least provide a guide to the relative disutility that could be expected.

Given that the injection site reactions were generally quick to resolve and impacted a small proportion of patients, if included in the economic evaluation it would not be expected to materially impact the ICERs across three populations presented.

This approach is also consistent with the omalizumab appraisal (see Boye et al, 2011[1]) where the impact of injection site reactions was not included in the economic modelling.

B11. Given the increased risk of mortality following hospitalisation as age increases observed in Roberts 2013, (0.0045 between 45 and 54 and a rate of 0.0278 at 65 years and over) please provide a rationale for grouping all patients aged 45 and over and assuming one rate of mortality. If possible, please provide exploratory analyses to assess the impact on the ICER of increased rates of mortality by age that would be consistent with the data presented in Watson 2007.

Watson 2007 states: "Mortality that occurred during the admission spell (the period from a live admission to either discharge or death) was reported per asthma admission code and stratified where appropriate by gender and age band: 0–11, 12–16, 17–44, ≥45. These age bands were selected based on common prescribing banding for asthma medications and to also categorise patients by age groups that have differing mortality and morbidity risks in the general population, as it important to assess if age differences occur in a clinical population". Based on the information provided in the publication, no further stratification can be made in age group ≥45, hence why the risk of mortality was grouped in the analysis as it is when the analyses are based on the Watson data. Please note that the sensitivity analyses which were conducted using Roberts et al, do use the stratifications, as published, for people aged 45-54, 55-64 and 65 years.

Exploratory analyses have been conducted to differentiate mortality risk by increasing age, however, it is not possible to obtain an accurate risk of mortality for the age group 45-54, 55-64 and 65 years and above, using the data published by Watson et al, and so these exploratory analyses should be interpreted with caution.

Two exploratory analyses were conducted because various assumptions need to be applied, which led to different approaches being taken and which gave different resulting probability estimates. The first approach takes the probability of mortality from Roberts and Watson for the age group 35-44 years, which are both known, and extrapolates probabilities for Watson, based on the ratio between the probabilities in Roberts over the age groups, to give corresponding hypothetical probabilities for Watson (please see Table 42).

Table 41: Option 1 - probabilities based on the ratios compared to the age group 35-44

Age group	Roberts 2013		Watson 2007	
35-44	0.0020	Ratio	0.0038	Ratio
45-54	0.0045	2.23	0.0085	2.23
55-64	0.0127	6.34	0.0243	6.34

[1] (Ref: Boye, KS., Matza, LS., Walter, KN. et al. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. *Eur J Health Econ* (2011) 12:219–230)

≥65	0.0278	13.81	0.0529	13.81

The second option estimates probabilities based on the number of deaths and hospitalisations reported for the age group 45 years and above, and the ratios between the probabilities from Roberts (Table 42). For example, it was assumed here that the number of hospitalisations observed in the total age group (>45), was equally divided over the different sub-categories. Based on the ratio observed in Roberts, the total number of deaths (n=177) was re-distributed to closely match the ratio, resulting in the probabilities presented below.

Table 42: Option 2- Probabilities based on number of deaths and hospitalizations reported for the ≥45 group and the ratios in Roberts

Age group	**Roberts 2013**		**Watson 2007**			
	p	Ratio	p	Ratio	n	N
45-54	0.0045		0.0076		18	2381
55-64	0.0127	2.84	0.0214	2.83	51	2381
≥65	0.0278	6.20	0.0454	6.00	108	2381

The results from the exploratory analyses are shown in Table 43 below. As previously mentioned, the results from these exploratory analyses should be interpreted with caution.

Table 43: Option 1 and 2 ICERs

	ITT					GSK proposed population excluding mOCS users with <4 exacerbations					GSK proposed population				
	Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)	Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)	Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)
Option 1															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£41,314	[redacted]	[redacted]	[redacted]	[redacted]	£20,203	[redacted]	[redacted]	[redacted]	[redacted]	£26,648
Option 2															
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£42,728	[redacted]	[redacted]	[redacted]	[redacted]	£20,735	[redacted]	[redacted]	[redacted]	[redacted]	£27,544

B12. Please provide the ICER if the mapped utility were used but no other disutilities from exacerbation or hospitalisations were applied. This would provide a bound on the impact of double counting of adverse events.

This analysis was performed by setting the utility decrement to 0 on the utility sheet in the model, in rows 33/35, and the results can be found in Table 44.

Table 44 The impact of applying only the mapped utility, with no other disutilities from exacerbations or hospitalisations applied.

	ITT					GSK proposed population excluding mOCS users with <4 exacerbations					GSK proposed population				
	Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)	Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)	Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)
Mepo + SoC	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£33,311	[redacted]	[redacted]	[redacted]	[redacted]	£16,010	[redacted]	[redacted]	[redacted]	[redacted]	£20,426

As seen in Table 44, removing the disutility applied for an exacerbation event, to explore the possible impact of double counting, causes the ICER to increase by a relatively small amount across each of the three populations. This is driven by the reduction in overall incremental QALYs. However, the ICER for the GSK proposed population (as well as the other populations presented) still remains within an acceptable cost-effectiveness threshold.

B13. Please clarify why the exacerbation rate for patients not meeting the continuation criteria is not calculated from the MENSA trial but rather assumes the same exacerbation rate as for SoC. Please provide the ICERs where the MENSA data used instead.

Patients not meeting the continuation criteria revert back to SoC alone (in MENSA) and experience the same exacerbation rates as the SoC group, from that point onwards.

There were two key reasons why the exacerbation rate for patients not meeting the continuation criteria is not taken from the mepolizumab arm of MENSA but assumes the same exacerbation rate as for SoC alone of MENSA. Firstly, in clinical practice if a patient discontinues on mepolizumab they remain on SoC alone. We thought that by applying the mepolizumab exacerbation rate of those not continuing on mepolizumab, may carry over any possible mepolizumab 'residual effect' that would not reflect patients in clinical practice when mepolizumab treatment is discontinued. This mirrored the approach taken in the NICE MTA of omalizumab.

B14. Please clarify why the 0.004 annual asthma mortality rate reported by de Vries 2010 was assumed to equal the mortality rate following an exacerbation?

The 0.004 annualised asthma mortality rate reported by de Vries is only used in the model where a like-NICE omalizumab MTA approach is selected – taking the mid-point of de Vries and Watson +15%. When this source is selected, the same mortality rate is applied to any exacerbation event. This differs from the application in the NICE omalizumab MTA where mortality is applied to the entire patient cohort. However, given the variation in the reported mortality rate and considering that severe asthma patients should be under the care of a tertiary care specialist, this was deemed most appropriate, to capture the risk but not to over apply it.

B15. Please clarify what evidence is available to support the assumption that the proportion of patients meeting the continuation criteria at 32 weeks (from the MENSA trial) would be maintained at 52 weeks.

In order to answer this question, the completed mepolizumab OLE, COSMOS provides the most appropriate source of long-term efficacy for mepolizumab (note that COLUMBA is ongoing). Patients recruited to COSMOS had either completed MENSA or SIRIUS and were treated with controller medication. At the exit of patients from MENSA the annualised exacerbation rate was 0.91. Those previously on the SoC alone arm were commenced on 4-weekly 100mg SC mepolizumab.

The annualised exacerbation rate for COSMOS patients that continued on mepolizumab remained stable throughout the trial (0.91 at week 0-32 [double blind], 0.92 for weeks 32 to 52 [open label] and 0.92 for weeks 52 to 84 [open label]. The rate of exacerbations per year

for the subjects who were previously treated with SoC alone in MENSA and switched to mepolizumab decreased over time during COSMOS from 1.94 to 1.04 per year. For the overall population i.e. including those patients previously in the placebo arm the rate was 0.93 (95% CI 0.83, 1.04).

In relation to withdrawals, 10% of COSMOS subjects were withdrawn (66/651) of which 19 (3%) were recorded as due to lack of efficacy.

Overall, based on the available evidence it does not appear to be unreasonable to assume that patients meeting the continuation criteria (based on an annualised exacerbation rate from a 32 week trial) be maintained at 52 weeks and further the model assumes a year-on-year 10% discontinuation rate post the 12 month continuation review. This to some extent reflects likely clinical practice where over time patients discontinue treatment based on risk benefit profile (e.g. possible reasons including lack of efficacy, personal preference, AEs).

Section C: Textual clarifications and additional points

C1. Page 15. Please clarify the meaning of a "like-NICE" approach?

The "like-NICE" approach refers to the ICER £15,645 / QALY gained which included the mortality assumptions we believe were applied by the Assessment Group in the NICE omalizumab MTA. Please refer to the main submission document Section 5.3.6 Mortality *iii) Mortality scenario analysis: NICE omalizumab MTA (TA278) – approximated approach; Watson 2007 + De Vries 2011 +15%*, Page 203. The ICER is reported in Table 147, page 246.

C2. Table 6 page 31. There are two asterisks. Please clarify if "" in the table relates to footnote *** If this is the case, please clarify what the second footnote denoted "*" relates to?**

It's difficult to see the asterisks; there are three labels - *, **, ***

* = Studies with mild and/or moderate asthma patients were excluded in this review. Studies with moderate/severe asthma patients were included, if the majority of the patients had severe asthma (see protocol deviations below and in the full systematic review report).
    - This refers to *Population*, exclusion criteria, in Table 6.

** = Other comparators included in the systematic literature review, but not reported in this submission include: reslizumab, benralizumab, tralokinumab, lebrikizumab, dupilumab and tiotropium.
    - This refers to *Intervention* inclusion criteria and *Study Design* inclusion criteria, in Table 6.

*** = RCT data were only extracted from publications which report primary results. Systematic reviews were screened for references to relevant RCTs, but data was not extracted from this source.
    - This refers to *Study Design* inclusion criteria, in Table 6.

C3. Table 14 page 62. Please confirm that the figures in column 3 (75mg) - it states 129 (84%) completed, and 130 (85%) entered the follow-up phase - are correct.

Yes the data are correct.

C4. Table 36 page 95. Please clarify the estimate for the RR of Mepolizumab 75 mg IV for exacerbations requiring hospitalisation/ED visits, as the current estimate falls outside of the confidence interval.

Thank you for highlighting this. The rate ratio for the mepolizumab 75mg IV arm is 0.68 as shown in Table 36. However, the correct confidence intervals for this arm are 0.33 and 1.41 (not 0.33 and 0.41 as shown in the submission).

C5. Table 27 page 32. There is no footnote 3. Please clarify whether this starts at the second "Note:"?

Yes, footnote 3 does start at the second "Note".

C6. Page 115. It is stated "trend confirmed by reduced times to first exacerbation". Please clarify if this should be "increased time to first exacerbation"?

Thank you for highlighting this. Yes, this should have read "increased time to first exacerbation".

C7. Page 142. Please check and clarify whether the reference to Table 63 should be to Table 67. Also "Table 67 and 68" on page 143 should be 68 and 69? Tables 64 and 65 on page 146 should refer to Tables 72 and 73?

Yes, apologies for the confusion
Reference to Table 63 *should be to Table 67* on page 142.
Reference to Table 67 and Table 68 *should be Table 68 and Table 69* on page 143.
Reference to Table 64 and Table 66 *should be Table 72 and Table 73* on page 143.

C8. Page 132/133. Please clarify what is the "population feasibility" section referred to in the table footnote?

Cross-referencing error. "Population feasibility" section referred to the footnote of Table 58 should refer to the narrative provided in Section 4.10.2 Study Selection, sub-heading *Patient population* on page 128. This provides information on the population for which it was feasible to conduct an NMA and introduces the three populations 'Overlap', 'Extended overlap' and Full trial'.

C9. Table 97 page 185. Table from Sonathi et al onwards – the data appears to be in the wrong columns. Please provide a corrected table.

Thank you for highlighting this. A corrected Table 97 from page 183-186 of the main submission is provided below.

Table 97. Summary of the 15 economic evaluations identified from the systematic literature review

Reference	Model	Intervention	Population	Outcome	Summary results
1. Oba and Salzman 2004[148] US (Third-party payer)	Cost-effectiveness analysis Used individual patient level data	Usual care: ICSs plus rescue medication	Adolescents (≥12 years) and adults with moderate-to-severe allergic asthma, uncontrolled despite ICSs, average age of 39 years, 54% female)	Cost per 0.5-point increase in the AQLQ score	$ 378 per 0.5-point AQLQ increase
				Cost per successfully controlled day (SCD)	$ 525 / SCD
2. Dewilde et al. 2006[153] Sweden (societal)	Cost-utility 5-state Markov model	Optimized Standard therapy at GINA step 4: high dose ICS plus LABA and additional rescue medication	Severe persistent asthma patients, average age of 43 years, 68% female Response to omalizumab was assessed at 16 weeks and it was assumed that non-responders reverted back to standard therapy	ICER	ICER = € 56,091/ QALY gained
3. Brown et al. 2007[154] Canada	Cost-utility 5-state Markov model	Standard therapy (high-dose ICS plus LABA and additional controller medication if required)	Canada (health-care payer) Patients with severe persistent allergic asthma despite high-dose ICS plus LABA	ICER	ICER = € 31,209/ QALY gained
4. Wu et al. 2007[155] USA	Cost-effectiveness and cost-utility analyses 3-state Markov model	ICSs with quick relievers alone	US (societal) Adult patients with severe uncontrolled asthma	ICER	ICER = $ 821,000/ QALY gained
				Cost per Symptom-free day (SFD)	$120 per SFD gained
5. Campbell et al. 2010[156] USA	Cost-utility 6-state Markov model	Standard therapy : ICS plus rescue and additional medication as required	US (US payer) Patients with moderate to severe persistent asthma, uncontrolled with ICSs, average age of 40 years, 60% female Response to omalizumab was assessed at 16 weeks and it was assumed that non-responders reverted back to standard therapy	ICER for base-case (and responders subgroup)	ICER= $ 287,200/ QALY gained ($ 172,300 / QALY gained)
6. Dal Negro et al. 2011[149] Italy	Cost-utility	Optimized standard therapy: high-dose ICS and LABAs (GINA 2014 step 4)	Italy (health-care payer) Patients sensitised to perennial antigens with severe difficult to treat asthma, who have been using omalizumab in addition to optimised therapy Response to omalizumab was	ICER	ICER= € 26,000/ QALY gained
				Cost per month with one FEV_1 predicted percentage point gained	€ 21.9 / %FEV_1
				Cost per month with one Asthma Control Test (ACT) point gained	€ 57.3/ ACT point gained

			assessed at 16 weeks and it was assumed that non-responders reverted back to standard therapy		
7. Dal Negro et al. 2012[150] Italy	Cost-utility	Standard therapy: Chronic high-dose antiasthma treatments including LABAs, OCS, Anti-LTs , antibiotics , SABAs, parenteral CS, xanthines	Italy (health-care payer) Patients (≥12 years) with severe, persistent atopic asthma. Average age of 45.4 years. 50% female.	ICER	ICER = € 23,880/ QALY gained
8. Morishima et al. 2013[157] Japan	Cost-utility 4-state Markov model	Placebo plus standard therapy: high-dose ICS, LABA, theophylline, and leukotriene antagonists	Japan (societal) Patients (20-75 years old) with moderate to severe asthma. Average age 50 years. 50% women. Response to omalizumab was assessed at 16 weeks and it was assumed that non-responders reverted back to standard therapy	ICER (and responders subgroup)	ICER = US$ 755,200/ QALY gained (US$590,100 / QALY gained)
9. Levy et al. 2014[151] Spain	Cost-effectiveness and cost-utility analyses	Standard therapy	Spain (National Health System) Patients (>14 years) with uncontrolled severe persistent asthma. Average age 54. 70.2% women	ICER	ICER = € 26,864.89/ QALY gained
				Cost per exacerbation avoided	€ 462.08 per exacerbation avoided
10. Sonathi et al. 2014[160] Greece (societal)	Cost-utility analyses	Omalizumab vs. Standard therapy: primarily comprised ICS, LABA and SABA	Adult patients with severe allergic asthma.	ICER	Based on INNOVATE trial data ICER= € 27,888/ QALY gained Based on the RWE from a prospective observational study conducted in Greece ICER = € 27,255/ QALY gained
11. Suzuki et al. 2015[162] Brazil (private health-care system)	Cost-effectiveness	Omalizumab vs. Standard of care	Uncontrolled severe allergic asthma.	Incremental cost per clinically significant exacerbation (CSE) avoided	BRL 9,289/CSE avoided
				Incremental cost per clinically significant severe exacerbation (CSSE) avoided	BRL 17,597/CSSE avoided
12. Willson et al. 2014[158] UK	Cost-utility analyses	Tiotropium vs. Usual care (high-dose ICS/LABA)	Asthma patients who were poorly controlled, confirmed by an Asthma Control	ICER	ICER = £21,906/QALY gained

(National Health System)			Questionnaire 7 (ACQ-7) score of 1.5 or greater despite usual care comprising at least a high-dose ICS/LABA. Average age 53.*		
13. Bogart et al. 2015[161] US (health-care payer)	Cost-utility analyses	Intervention and comparators are not explicitly reported in the abstract provided	Adult with severe refractory asthma.	ICER	Mepolizumab without bronchial thermoplasty was the most cost-effective option for biologics responders ICER = $ 21,388/ QALY gained Among patients who do not respond to biologic treatment, bronchial thermoplasty is a cost effective treatment option ICER = $ 33,161/ QALY gained
14. Norman et al. 2013[152] UK	Cost-utility analyses	Omalizumab versus standard therapy Step 4 (high dose ICS and LABA) and Step 5 (frequent or continuous OCS treatment)	Adults and adolescents (≥12 years old) with severe uncontrolled asthma	ICER	£83,822/QALY gained
				Hospitalisation sub-group; those hospitalised 12 months prior to trial entry	£46,431/QALY gained
				Maintenance OCS subgroup	£50,181/QALY gained
15. Faria et al. 2014 UK	Cost-utility analyses	Omalizumab versus standard of care; optimised therapy at step 4 or 5	Severe persistent allergic asthma patients (≥12 years) uncontrolled at Step 4 and in the process of moving up to Step 5 and patients controlled at Step 5 whose asthma would be uncontrolled if they were on Step 4 therapy		

(*)Both treatment arms included an 'early response phase' transition matrix reflecting weekly transition probabilities across the first 8 weeks of the trial duration and was applied for the first eight cycles of the cost-effectiveness model. A 'late response phase' transition matrix reflecting weekly transition probabilities across the remaining 40 weeks of the clinical trial duration was also included in the cost-effectiveness model for both treatment arms. The 'late response phase' transition matrix was applied from the ninth cycle of the cost-effectiveness model and was used to extrapolate effectiveness over the remainder of the time horizon.

XX Considered relevant and discussed further in the main body of the submission; see section 5.1.2

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Mepolizumab for treating severe eosinophilic asthma [ID798]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Asthma UK

Your position in the organisation: [redacted]

Brief description of the organisation: Asthma UK is the UK's leading asthma charity. We support people with asthma when they need us the most and fund world-leading research to find better treatments and ultimately a cure. Our goal is to prevent asthma attacks, especially those that result in death and emergency hospitalisation.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: Asthma UK receives no funding from the tobacco industry.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Asthma is one of the most prevalent long-term conditions in the UK, with 5.4 million people currently receiving treatment. Severe asthma affects nearly 5% of people with asthma – around 250,000 people, of whom a subgroup will have an eosinophilic phenotype. The National Review of Asthma Deaths highlighted that almost 40% of those who died had severe asthma.[1]

This is a specific type of asthma, rather than simply an extreme form of the condition. It does not respond to standard treatment and requires more intensive and expensive therapies to control symptoms to prevent attacks, hospitalisations and deaths. People with the most severe asthma represent a particular challenge: they not only suffer greater morbidity, but they also fall outside the robust evidence base that informs most asthma care, requiring specialist attention, treatment and pathways.[2]

[1] Royal College of Physicians. Why asthma still kills: The National Review of Asthma Deaths; 2014.

[2] Wenzel S. Characteristics, definition and phenotypes of severe asthma. In: Chung KF, Bel E, Wenzel S, editors. ERS Monograph: Difficult-to-Treat Severe Asthma. 51: European Respiratory Society; 2011.

Ongoing severe symptoms and a complex medicine regime are often accompanied by frequent hospital admissions for many people with severe asthma. Numerous hospital admissions to respiratory wards, intensive care units (ICU) and high dependency units (HDU) lead to further social isolation and economic disadvantage for people affected by asthma as well as high costs to the NHS.

In November 2015, we asked a number of people with severe asthma for their experience on living with the condition. Around 50 people responded, and a selection of their views is presented below.

"[Severe asthma] affects me every day, simple everyday things are triggers, going out places can be difficult due to strong fragrances, air fresheners, dust, mould spores, pollen and so very much more. A simple cold can go straight to your chest and end you up in hospital fighting for your life. The steroids we have to take affects your body badly and can cause multiple illnesses, yet it's one of the only things that helps with the swellings in the airways. Sleeping is a nightmare, when you manage to get any sleep you often wake up gasping for breath as you're going into a full attack."

"Every day has to be planned regimentally in advance when you are dependent on nebulisers (battery ones just aren't as strong). At the same time though, you can't make plans in advance because your chest can kick off at any time and plans often have to be cancelled last minute."

"I am still very nearly housebound because I can't breathe well enough to walk more than a few steps much of the time. I get out an average of twice a week at the moment, have had to give up work, move home etc, because my body simply won't allow me to live what would usually be considered a normal life."

"Life is chaotic with severe asthma. It can be impossible to work as you cannot commit to a regular schedule - I cannot go out if it is raining, humid, low temperatures, foggy, pollution levels or pollen are high, because of the risk of attack…yesterday I did a food shop, today I can't walk from the lounge to the kitchen to make a drink but I have taken the same medications today that kept the condition under control yesterday. We bear a huge psychological

burden living in fear of the next attack and watching our families struggle to cope with our illness. There is no cure, little control, financial hardship - including having to pay for medicines and constant rounds of hospital/doctors appointments."

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Keeping symptoms under control is the main goal of asthma treatment, but the reality for some people with severe asthma is that this is not possible with current standard treatments.[3] It is therefore important for new treatment options to help people better control their symptoms to prevent potentially life-threatening asthma attacks.

People with severe asthma have to find a way to cope with dangerous and frustrating symptoms. Persistent symptoms can lead to lack of sleep, social isolation, feelings of despair and depression, low activity levels, weight gain and increased dependence on family and carers. [4]

As highlighted from comments we have received from people with severe asthma, many people are concerned at the ineffectiveness of current treatments to maintain control, in addition to the side-effects associated with treatment.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Specialised centres, commissioned by NHS England, are fundamental to the successful delivery of severe asthma care, using innovative care models to ensure appropriate diagnosis, and use of existing and new high-cost medications.

[3] Hotgate ST and Polosa R, The mechanisms diagnosis and management of severe asthma in adults *Lancet* 2006, 368: 780-93

[4] Asthma UK. Fighting for Breath; 2011

People with severe asthma can often find themselves taking very high doses of medicines for a long time. The side effects of these medicines, especially long-term oral corticosteroids, are often very serious. These include osteoporosis, psychological symptoms, Cushing's syndrome, adrenal failure, diabetes, growth retardation, high blood pressure, cataracts and Addison's disease.[5,6,7,8]

Research evidence assessing rates of side effects from oral corticosteroids specifically among people with severe asthma is limited, though a meta-analysis of their use in people with inflammatory diseases found an average adverse event rate of 150 per 100 patient-years, with much higher rates in some groups.[9]

In reaching out to people with severe asthma for their views on living with the condition, several highlighted their experience of current care and treatments – with many concerned at the side-effects. These are presented below:

"It's terrifying. Not knowing when you're going to next be in hospital. You can't make plans for fear of having to cancel. Your body is distorted from all the medication and you end up on more medication to deal with the side effects of the medication that keeps you alive…It feels like a life sentence at times and not only to you but to your family too. Unless you live with severe asthma you have no idea what it is like."

"Every day seems to be an uphill struggle to control asthma symptoms…it's always hard to breath and taking inhalers and tablets for Asthma on a daily basis just to survive can be daunting...and when you have an attack it can be quite scary…having to have a nebulizer and steroid treatment can take its toll on your body…steroids change your personality and I become aggressive on them"

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[5] Stuart FA, Segal TY, Keady S. Adverse psychological effects of corticosteroids in children and adolescents. Arch Dis Child. 2005 May;90(5):500-6.
[6] Weldon D. The effects of corticosteroids on bone growth and bone density. Ann Allergy Asthma Immunol. 2009 Jul;103(1):3-11;, 50.
[7] Blackburn et al, Quantification of the Risk of Corticosteroid-induced Diabetes Mellitus Among the Elderly, J Gen Intern Med. 2002 September; 17(9): 717–720.
[8] BTS/SIGN op cit
[9] Hoes JN et al, Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis. 2009 Dec;68(12):1833-8. Epub 2008 Dec 9.

"I have reached a point where the side-effects of treatment (steroid side-effects, insomnia, weight gain, fungal infections, concerns and tests regarding bone density etc) are becoming almost as persistent and unpleasant as the asthma symptoms they are treating."

"Much of the day can be taken up with nebulised treatments, frequent taking of medications – for me that is 13 different prescriptions, some taken more than once a day."

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Unfortunately, we have not received views to-date from people with severe eosinophilic asthma that have been treated with mepolizumab. However, as mentioned above people with severe asthma are consistently concerned with the difficulty in maintaining control using the current treatments available, in addition to the side-effects that they experience.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

There is a substantial unmet need for people with severe asthma in the treatment options available to them. People with severe asthma have very limited treatment options that involve high doses of drugs with very poor side

effect profiles. Mepolizumab could provide an alternative option for people with severe eosinophilic asthma that do not respond well to current treatments.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

N/A

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Please see the response above to “Current practice in treating the condition”

Please list any concerns patients or carers have about the treatment being appraised.

N/A

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

N/A

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Around 250,000 people are estimated to have severe asthma, of which a subgroup will have an eosinophilic phenotype. This new treatment is specifically targeted to reduce severe asthma attacks by reducing the levels of blood eosinophils associated with the condition. It is therefore logical that this subgroup of people with severe asthma could potentially benefit more than the broader severe asthma group.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

As mepolizumab is targeted at reducing the levels of blood eosinophils associated with severe asthma, those with severe asthma who do not have an eosinophilic phenotype may benefit less from the treatment.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

N/A

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

N/A

9. Other issues

Do you consider the treatment to be innovative?

Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

As highlighted above, there is a substantial unmet need for people with severe asthma in the treatment options available to them. This treatment could offer an alternative and potentially more effective treatment option to a specific subgroup of those with the condition.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Severe asthma affects nearly 5% of people with asthma – around 250,000 people, of whom a subgroup will have an eosinophilic phenotype that might benefit from mepolizumab. The National Review of Asthma Deaths highlighted that almost 40% of those who died had severe asthma.
- People with severe asthma do not respond to standard treatment and require more intensive and expensive therapies to control symptoms to prevent attacks, hospitalisations and deaths. There is a substantial unmet need for people with severe asthma in relation to treatment options.
- People with severe asthma can often find themselves taking very high doses of medicines for a long time. The side effects of these medicines, especially long-term oral corticosteroids, are often very serious and of great concern and distress to people with severe asthma.
- Ongoing severe symptoms and a complex medicine regime are often accompanied by frequent hospital admissions for many people with severe asthma.

- This treatment could offer an alternative and potentially more effective treatment option to those people with severe asthma that have an eosinophilic phenotype.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Mepolizumab for treating severe eosinophilic asthma [ID798]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:

Name of your organisation: British Society for Allergy and Clinical Immunology (BSACI)
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NIL

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Mepolizumab for treating severe eosinophilic asthma [ID798]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The mechanisms leading to asthma are heterogenous with considerable variations in severity and complexity best expressed as the relationship between airway dysfunction as measured by variability in lung function and airway inflammation as measured by induced sputum, exhaled nitric oxide, a blood eosinophil count or other measures of TH2 like inflammatory responses. Increased number of eosinophils in the airway and blood are found in asthma reflecting a Th2 pattern of inflammation which leads to the production of increased amounts of a cytokine called IL-5 which is a specific growth factor for eosinophils. IL-5 is released by Th2 lymphocytes and a new class of innate cells called innate lymphoid cells type 2. In most patients with asthma the allergic response results in increased amounts of specific IgE. However in a significant proportion of asthmatics particularly those with adult-onset asthma the eosinophilia occur without increased IgE. The mechanism driving this inflammatory process in this group of patients is not clear although the likelihood is that it is a non-IgE-mediated ILC2 mediated process driven by environmental stimuli. In both IgE and non-IgE mediated asthma the process is driven by IL-5 and inhibited by mepolizumab. The degree of eosinophilia associated with asthma varies considerably with a proportion of patients including those of adult-onset having a marked blood and tissue eosinophilia. It is likely these patients will do particularly well with mepolizumab.

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Mepolizumab for treating severe eosinophilic asthma [ID798]

Mepolizumab is currently unlicensed and not available in the UK. Therefore it's place within clinical guidelines is not established.

Eosinophilic asthma is the mechanism associated with the most severe form of asthma and the most difficult to treat. A high proportion of those requiring ventilation have eosinophilic asthama. The recently published National Review of Asthma Deaths established that at least 15% of those who died from asthma had evidence of eosinophilia and this is likely to be an underestimate.

Mepolizumab is effective in preventing severe exacerbations in people with eosinophilic airway disease. The more eosinophilic they are the more they will benefit. Eosinophilic inflammation is often disconnected from the traditional symptom pattern of asthma (it can be clinically silent for periods of time), and the physiological abnormalities associated with asthma. The indications for the use of mepolizumab have to reflect the pattern of asthma where it will be of most benefit and should include people with an exacerbation prone endotype who may not necessarily demonstrate typical asthma symptoms or variable airflow obstruction. It is critical therefore that severe eosinophilic asthma is broadly defined as people with severe exacerbation prone eosinophilic airway disease as measured by exhaled Nitric oxide and/or sputum and/or blood eosinophilia.

In the majority, eosinophilic inflammation can be prevented by inhaled steroids and treatment failure may be due to sub-optimal adherence. While it is reasonable for mepolizumab to be used as an alternative to regular oral steroids it will be essential to objectively establish that patients are compliant with their inhaled treatment before mepolizumab is considered .

Because of high cost of this technology it is most appropriate for mepolizumab to be initiated and monitored in tertiary care.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the

trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The infrastructure for delivery of mepolizumab is already in place in tertiary centres because of their longstanding experience with omalizumab.

The evidence base suggests that response will depend on careful selection of patients. Those with an eosinophilic driver to their asthma will benefit but not other asthma patients even if they have severe disease. Therefore considerable expertise will be required to select appropriate patients for this technology ensuring that they have the clinical features compatible with eospinophilic asthma backed up with direct evidence of airway eosinophilia (bronchial biopsy or induced sputum) or indirect evidence (blood count eosinophilia, elevated exhaled nitric oxide).

From published studies it is likely that response to treatment may require a trial of treatment of 4-6 months and using the model already established for omalizumab – treatment can either be stopped or continued with annual reviews of response undertaken.

Mepolizumab has a very good safety profile. The evidence would suggest that even after several years treatment on stopping patients rapidly return to their baseline although the data on this is so far limited

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

There are unpublished on-going trials with mepolizumab which may provide additional insight into the use of this technology during the technology appraisal.

Implementation issues

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Mepolizumab for treating severe eosinophilic asthma [ID798]

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Some additional resource may be required however overall it is likely that targeted use of mepolizumab will reduce exacerbations of severe asthma and hence hospital admission. Therefore resource can be redirected to be more out-patient focussed and preventative rather than reactive. This will benefit patients and improve quality of life.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

This will be similar for all biologics used in an outpatient setting and therefore suggest consulting the omalizumab document. Overall however this technology is likely to reduce inequality.

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Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: Royal College of Pathologists
Are you (tick all that apply):

- *a specialist in the treatment of people with the condition for which NICE is considering this technology?*

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?

Steroids / beta agonists / theophyllines

Is there significant geographical variation in current practice?

No,

Are there differences of opinion between professionals as to what current practice should be?

Not really

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Xolair – alternative if IgE elevated and perennial aeorallergy
Ads – low toxicity / well tolerated, good response in high percentage of eligible patients
Disads – very tight criteria for prescribing, many patients with clear allergic asthma are excluded as IgE too high

Steroids –
Ads - highly effective at reducing eosinophilia and exacerbations
Disads – severe long term toxicity and on going higher risk of infection

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Patients should be phenotyped by blood / sputum / BAL eosinophils

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Secondary care in specialist centres who phenotype patients and manage severe difficult to treat asthma

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
N./A

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

British thoracic society / SIGN – would likely be included at stage 4/5. Needs a comparison with Xolair to decide which drug should be used if eligible for both – need comparison between the two and knowledge of cost and safety.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If introduced in specialist centres no additional requirements or training

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

BTS stage 4/5 with eosinophilia. Some decision will need to be made on what eosinophil count is counted as high.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

NA

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

NA

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NO

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Currently this group of patients have a treatment (steroids) but there are significant long term complications and a steroid sparing agent is desperately required to prevent long term complication.

No extra resources should be needed if blood eosinophil count to be used for phenotyping. If sputum or BAL considered other laboratory diagnostics may be needed

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

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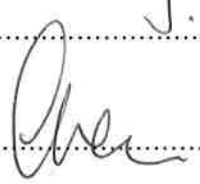
Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the submission provided by **the BSACI** and consequently I will not be submitting a personal statement.

Name: J. NASSOR

Signed: 

Date: 2/3/16.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Mepolizumab for treating severe eosinophilic asthma [ID798]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Professor Andrew Wardlaw

Name of your organisation
University of Leicester and University Hospitals of Leicester NHS Trust

Are you (tick all that apply):

X a specialist in the treatment of people with the condition for which NICE is considering this technology?

X a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

I have no links to the tobacco industry

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

1) How is the condition currently treated in the NHS

Asthma is a common condition effecting about 5% of the adult population. In most people is controlled with modest doses of inhaled corticosteroids (IHC) and beta 2 agonists. However about 5% of people with asthma have more difficult to control disease with major effects on quality of life and an increased risk of severe exacerbations leading to hospitalisation and occasionally avoidable death. These patients require increased amounts of treatment including frequent courses of (or maintenance) oral corticosteroids. Corticosteroids carry a high burden of side effects including hypertension, osteoporosis, obesity, diabetes, skin thinning, mood change, cataracts and easy bruising. These patients make up a significant workload for respiratory physicians throughout England and Wales. A network of specialist difficult asthma clinics have been established for a number of years and these are being organised into a geographically uniform group of national commissioning centres for specialised asthma care by NHS England. These will act in a hub and spoke model to lead the diagnosis and management of these often complex patients.

Management of difficult asthma is based on a detailed assessment using, as much as possible, objective criteria to measure physiological abnormalities, combining this with a holistic assessment of the impact of symptoms on the patient's quality of life. With difficult asthma it is essential to assess the contribution of extra-pulmonary factors such as psychological problems, sub-optimal adherence, alternative diagnoses

including various patterns of dysfunctional breathing and co-morbidities to the patients symptoms before assessing what additional treatments are required.

Treatment is based on the British Thoracic Society guidelines for the management of chronic adult asthma with escalation in a step-wise fashion including stopping treatments which are not tolerated or are ineffective. Asthma can cause a number of pathophysiological abnormalities including variable airflow obstruction (VAO) leading to episodic breathlessness, airway inflammation which is generally eosinophilic and associated with severe exacerbations and chronic breathlessness and recurrent infections caused by lung damage from chronic disease, often in the context of allergic fungal airway disease. Bronchodilators such as beta 2 agonists are effective in the treatment of variable airflow obstruction, corticosteroids are effective in suppressing eosinophilic inflammation and therefore exacerbations. Neither are very effective in managing the symptoms of lung damage which requires pulmonary rehabilitation and control of bacterial and fungal bronchitis. In the majority of asthmatics VAO is caused, at least in part, by the inflammatory process although VAO and inflammation can occur independently in some people especially in those with 'hypereosinophilic' asthma who have most to gain from mepolizumab. There is very good evidence that active eosinophilic inflammation is a major risk factor for severe exacerbations of asthma and that normalisation of the sputum eosinophil count with corticosteroids greatly reduces that risk. The mainstay of the prevention of exacerbations is therefore inhaled corticosteroids (IHC). However in some individuals the inflammatory process is such that even high dose, potent IHC are insufficient to control eosinophilic inflammation and maintenance systemic steroids are required. Even then breakthrough exacerbations can occur. In these cases the therapeutic choices are limited essentially to omalizumab (anti-IgE therapy). Prescription of omalizumab is limited by the need for IgE sensitisation to a perennial allergen. Many patients with 'hypereosinophilic' asthma are of adult onset and non-atopic. There is no evidence base for other steroid sparing treatments such as methotrexate, azathioprine and mycophenolate which are generally disappointing when used off licence.

2. Subgroups who will benefit

Mepolizumab is a biological therapy that reduces eosinophilic inflammation by inhibiting the activity of the eosinophilic growth factor IL-5. It is well tolerated and has a very specific mechanism of action. It is therefore only effective in people with eosinophilic asthma and generally speaking the more eosinophilic the patient (measured as either a sputum or peripheral blood eosinophilic count) the more likely it is that they will benefit. It reduces the risk of exacerbations by about 50% and has a significant steroid sparing effect in those requiring maintenance corticosteroids, but has much less effect on day to day symptoms. It will therefore be most effective in people with a tendency to exacerbate, but who are relatively well in between their asthma flares.

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3. Setting in which the drug should be used

The treatment should be prescribed after a detailed assessment in a clinic specialising in the management of difficult asthma. The clinic should be accredited by NHS England as able to manage difficult asthma and be part of the BTS severe asthma network. The treatment needs to be given in a secondary care setting because of the risk of anaphylaxis, but treatment can be devolved to the referring hospital.

4. Guidelines

As a new treatment there are no current guidelines for mepolizumab in asthma, but it is well recognised that there is an important unmet need for patients with severe eosinophilic asthma with recurrent severe exacerbations requiring frequent courses of oral steroids or maintenance treatment.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

1. Comparison with current treatments

Mepolizumab represents a significant advance in the treatment of patients with severe eosinophilic asthma. It is effective and well tolerated and will significantly reduce hospitalisation for asthma and the burden of side effects from corticosteroids. The only other comparable treatment at the moment is omalizumab which is restricted to

people with allergic asthma with a certain total IgE/weight ratio and is not always effective at preventing exacerbations.

2.0 Treatment parameters

Before starting treatment the following criteria should be fulfilled

a) The patient should be assessed in a centre with expertise in the diagnosis and management difficult asthma. This should confirm the diagnosis of severe asthma and exclude extra-pulmonary causes for the patient's difficult to control disease.

b) Confirmation of adherence to inhaled and if appropriate oral corticosteroids should be confirmed by objective assessments including prescription refills, measurement of serum corticosteroids and cortisol and suppression of exhaled nitric oxide using an inhaler device that monitors compliance.

c) A history of three severe exacerbations (defined as a deterioration in asthma control requiring a course of oral corticosteroids lasting at least three days) in the previous 12 months or a requirement of maintenance (>6 months) oral corticosteroids equal or greater than 5mg/day.

d) Evidence of eosinophilic asthma as defined by a sputum eosinophil count of a certain degree or a peripheral blood eosinophilic count of greater than a certain threshold within a given time window.
The normal sputum eosinophil count is less than 2%. Patients with a sputum eosinophilia of greater than 3% have been shown to be at risk of exacerbations and respond to mepolizumab. A sputum eosinophil count of greater than 5% would increase the specificity of the response to mepolizumab. Deciding on the optimal threshold for the peripheral blood eosinophilia is critical as this will be used more often than sputum as a biomarker for eligibility for treatment. The higher the peripheral blood eosinophil count the more likely it is the patient will benefit, but increased specificity will result in decreased sensitivity with some people who would benefit missing out. I think the level should be set at around 0.4 x 109/L. In terms of the time window for evidence of an eosinophilia this should be reasonably long (perhaps as much as 5 years), as many patients who will benefit from mepolizumab will be on maintenance oral steroids which will suppress evidence of active eosinophilic inflammation.

e) Similar to omalizumab it is important that the efficacy of mepolizumab is reviewed after an appropriate time to see if it has worked. The aim of treatment (either a reduction in severe exacerbations or a steroid sparing benefit) should be explicitly stated before treatment is started and the success of the treatment measured against those aims after six months of therapy. The treatment should be stopped if the aims have not been achieved. Where the outcome is in doubt a further six months should be

given and the efficacy formally reassessed. Thereafter efficacy should be formally reassessed on an annual basis.

3.0 Relevance of clinical trials to UK practice.

The clinical trials were very relevant and indeed the seminal proof of concept trial which was confirmed in subsequent phase 2b and 3 multicentre trials was carried out in the UK. The trials have been very consistent in showing about a 50% reduction in severe exacerbations, but a much lesser effect on day-to-day symptoms and lung function.

4.0 Adverse events

Mepolizumab appears very well tolerated with few significant adverse events. There is a small risk of anaphylaxis so it needs to be given in a hospital setting where resuscitation facilities are available.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

I don't believe there are any equality and diversity issues other than the need to attend hospital on a monthly basis for a couple of hours that might impact on people in work, or who have difficult with transport or child care.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be

information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I am not aware of any other evidence other than that in published trials or held by the company on file

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Mepolizumab will be delivered in a very similar way to omalizumab which most respiratory physicians with an interest in asthma and all asthma centres are very familiar with. Omalizumab is generally delivered in nurse led clinics alongside a difficult asthma clinic. The main problem will be capacity in terms of space and specialist nurse time to deliver a biological therapy to an increased number of people. In Leicester we have about 50 people on omalizumab at the moment and already have a database of around 50 people who we think will benefit from mepolizumab so that we will need to double our capacity to cope with demand. Having said that asthma

centres have had plenty of warning that mepolizumab is likely to become available by the autumn of 2016.

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Mepolizumab for treating severe eosinophilic asthma [ID798]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Asthma UK consequently I will not be submitting a personal statement.

Name: .....Lehanne Sergison .....

Signed: ..Lehanne Sergison.....

Date: .....16/02/12.....

Mepolizumab for treating severe eosinophilic asthma: A Single Technology Appraisal

Produced by School of Health and Related Research (ScHARR), The University of Sheffield

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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Contributions of authors

Katy Cooper, Sue Harnan and Chris Carroll summarised and critiqued the clinical effectiveness data reported within the company's submission. Iñigo Bermejo and Matt Stevenson critiqued the health economic analysis submitted by the company. Jean Sanderson critiqued the network meta-analysis and provided other statistical support. Mark Clowes critiqued the company's search strategy. Tim Harrison and Shironjit Saha provided clinical advice. All ScHARR authors were involved in drafting and commenting on the final report, the clinical advisors responded to individual questions posed by remaining team members.

CONTENTS

TABLES

FIGURES

Abbreviations

ACQ	Asthma Control Questionnaire
AE	Adverse Event
AQLQ	Asthma Quality of Life Questionnaire
ARM	Asthma-related mortality
AT	As Treated
ATS	American Thoracic Society
BNF	British National Formulary
BTS	British Thoracic Society
CS	Company Submission
CI	Confidence Interval
CrI	Credible Interval
CPRD	Clinical Practice Research Datalink
CVT	Cardiac, Vascular and Thromboembolic
DIC	Deviance Information Criterion
DREAM	Dose Ranging Efficacy And safety with Mepolizumab in severe asthma
ED	Emergency Department
EMA	European Medicines Agency
EQ-5D	EuroQol 5 Dimensions
ERG	Evidence Review Group
ERS	European Respiratory Society
FDA	Food and Drug Administration
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 Second
GSK	GlaxoSmithKline
GSK PP	GlaxoSmithKline Proposed Population
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
ICS	Inhaled Corticosteroids
ICU	Intensive Care Unit
IgE	Immunoglobulin E
ITT	Intention To Treat
IM	Intramuscular

IV	Intravenous
LABA	Long-acting Beta Agonist
LTRA	Leukotriene Receptor Agonist
MAR	Missing At Random
MCID	Minimal Clinically Important Difference
MD	Mean Difference
MENSA	Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma
mOCS	Maintenance Oral Corticosteroids
MTA	Multiple Technology Appraisal
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NRAD	National Report for Asthma Deaths
OCS	Oral Corticosteroids
PAS	Patient Access Scheme
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RR	Rate Ratio
SABA	Short-Acting Beta Agonists
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SGRQ	St. George's Respiratory Questionnaire
SIGN	Scottish Intercollegiate Guidelines Network
SIRIUS	Steroid Reduction with Mepolizumab Study
SoC	Standard of Care
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal

1 SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The decision problem is largely consistent with the National Institute for Health and Care Excellence (NICE) scope. The population in the scope and the company's submission (CS) is *"adults with severe eosinophilic asthma"*, whilst the licence is for *"severe refractory eosinophilic asthma"*. The intervention is mepolizumab (brand name Nucala®) in addition to standard of care (SoC). The licensed dose is 100mg delivered via subcutaneous (SC) injection every 4 weeks. Data for the 75mg intravenous (IV) dose are also included in the CS and in the Evidence Review Group (ERG) report, since it is stated in the CS and in the summary European Public Assessment Report (EPAR) for mepolizumab that the 100mg SC and 75mg IV doses show bioequivalence. Relevant comparators are SoC alone, or omalizumab for the subgroup of patients with both eosinophilic and allergic immunoglobulin E (IgE)-mediated severe asthma.

There is scope for disagreement in defining the relevant population in terms of degree of asthma severity and degree of eosinophilia. These factors are not explicitly defined in the NICE scope or the licence for mepolizumab. The CS suggests restricting mepolizumab use to a "GSK proposed population" (GSK PP) based on *post hoc* subgroup analyses of the pivotal trials (Section 1.2).

1.2 Summary of clinical effectiveness evidence submitted by the company

Pivotal trials: The clinical effectiveness evidence in the CS is based predominantly on three randomised controlled trials (RCTs) comparing add-on mepolizumab with placebo plus SoC in patients with severe eosinophilic asthma. Two trials (DREAM and MENSA) had a primary endpoint of reduction in exacerbations, whilst one (SIRIUS) enrolled patients receiving maintenance oral corticosteroids (mOCS) and had a primary endpoint of reduction in oral corticosteroids (OCS) use. In addition, data from two open-label extension studies (COSMOS and COLUMBA) enrolling patients from the three RCTs are included in the CS.

Key sub-populations: In addition to the intention to treat (ITT) populations of the three trials, the CS focusses on two "GSK proposed populations" based on exacerbation history, eosinophil count and use of mOCS. The ERG requested data on a fourth population. The populations, together with the abbreviated name used throughout this report, are:

- **Intention-to-treat (ITT) population:** All trial patients who were randomised and received at least one dose of study medication; this is actually a form of modified ITT (mITT) but this population is referred to in the ERG report as the ITT population for consistency with the CS.
- **GSK proposed population (GSK PP):** Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/μl at initiation of treatment; and ≥4 exacerbations

in the previous year and/or dependency on mOCS (regardless of exacerbations in previous year).

- **GSK PP excluding mOCS users with <4 exacerbations (GSK PP excl. stable mOCS):** Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/µl at initiation of treatment; and ≥4 exacerbations in the previous year.
- **mOCS users with <4 exacerbations (stable mOCS):** Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/µl at initiation of treatment and dependency on mOCS but <4 exacerbations in the previous year. This constitutes the patients in the GSK PP who are not within the GSK PP excl. stable mOCS (requested by the ERG).

The ERG notes that the term "stable" in relation to mOCS is used for ease of reading and refers to having fewer than four exacerbations in the previous year.

The company's rationale for the GSK PP is based on *post hoc* modelling and subgroup analyses of DREAM and MENSA, indicating a greater reduction in exacerbations for mepolizumab vs. placebo for patients with (a) higher baseline blood eosinophils and (b) more previous exacerbations. In addition, the CS includes mOCS users with eosinophils ≥150 cells/µl in the GSK PP (regardless of previous exacerbations) since mOCS users are likely to be a severe group and there are clinical benefits to reducing mOCS. The CS also provides data for the GSK PP excl. stable mOCS. The CS states that this population may show a greater reduction in exacerbations than the GSK PP since mOCS use may reduce exacerbations and so mOCS users with <4 previous exacerbations may have less potential to demonstrate a further reduction in exacerbations than non-mOCS users, or those with ≥4 previous exacerbations.

Key clinical effectiveness results: Clinically significant exacerbations were defined in all three trials as worsening of asthma requiring use of systemic corticosteroids (or double the maintenance dose) and/or hospitalisation and/or emergency department (ED) visits. The rate ratios (RRs) for clinically significant exacerbations for mepolizumab (100mg SC and 75mg IV groups combined) vs. placebo, meta-analysed across MENSA and DREAM, were: RR=0.51 (95% confidence interval (CI) 0.42, 0.62) for the ITT population; RR=0.41, 95% CI 0.31, 0.55) in the GSK PP; RR=0.35 (95% CI 0.25, 0.50) in the GSK PP excl. stable mOCS; and RR=0.55 (95% CI 0.32, 0.92) in the stable mOCS population. In SIRIUS, the OCS-sparing study, RRs for exacerbations were less favourable than in MENSA and DREAM: RR=0.68 (95% CI 0.47, 0.99) for the ITT population; RR=0.77 (95% CI 0.51, 1.17) in the GSK PP; RR=0.81 (95% CI 0.40, 1.64) in the GSK PP excl. stable mOCS; and RR=0.75 (95% CI 0.44, 1.29) for the stable mOCS population.

For exacerbations requiring hospitalisation, RRs for mepolizumab (100mg SC and 75mg IV groups combined) vs. placebo, meta-analysed across MENSA and DREAM, were: RR=0.50 (95% CI 0.28, 0.89) in the ITT population; RR=0.44 (95% CI 0.19, 1.02) in the GSK PP; RR=0.43 (95% CI 0.16, 1.12) in the GSK PP excl. stable mOCS; and RR=0.53 (95% CI 0.10, 2.75) in the stable mOCS population. In SIRIUS, hospitalisation numbers were low (ITT: 7 for placebo vs. 0 for mepolizumab). Exacerbations requiring hospitalisation or ED visits showed a similar pattern. In terms of quality of life, differences on the St. George's Respiratory Questionnaire (SGRQ) for MENSA and SIRIUS for mepolizumab vs. placebo ranged from 5 to 13 units ($p<0.001$ for meta-analysed results), in all sub-populations except stable mOCS (minimal clinically important difference [MCID] 4 units). Differences on the Asthma Control Questionnaire (ACQ) meta-analysed across MENSA and DREAM ranged from -0.3 to -0.8 ($p<0.001$ for all) across all sub-populations except stable mOCS (MCID 0.5 units). Differences for the Asthma Quality of Life Questionnaire (AQLQ, DREAM only) ranged from 0.1 to 0.4 (MCID 0.5 units) and were not statistically significant ($p>0.1$ for all).

Steroid reduction: The SIRIUS trial had a primary endpoint of percentage reduction in OCS dose whilst maintaining asthma control. Odds ratios (OR) for mepolizumab vs. placebo were: OR=2.39 (95% CI 1.25, 4.56) for ITT; OR=1.81 (95% CI 0.86, 3.79) for GSK PP; OR=2.75 (95% CI 0.72, 10.59) for GSK PP excl. stable mOCS. Absolute differences between mepolizumab and placebo for the proportion achieving a reduction in OCS dose whilst maintaining asthma control were 20% in the ITT population, 13% in the GSK PP, and 26% in the GSK PP excl. stable mOCS.

In terms of secondary outcomes in the GSK PP, the OCS dose was reduced by at least 50% in 48% of patients (mepolizumab) vs. 38% (placebo), giving an OR of 1.60 (95% CI 0.70, 3.64) and an absolute difference of 10%. A reduction in OCS dose to ≤5 mg was observed in 50% of patients (mepolizumab) vs. 40% (placebo), with an OR of 1.64 (95% CI 0.68, 3.93) and an absolute difference of 10%. In addition, OCS use was stopped completely in 13% (mepolizumab) vs. 8% (placebo), with an OR of 1.35 (95% CI 0.32, 5.78) and an absolute difference of 5%. Results were not significant in the GSK PP ($p>0.1$), though numbers were small. ORs and absolute differences were slightly more favourable in the ITT population than the GSK PP, and were generally statistically significant in the ITT population. Results in the GSK PP excl. stable mOCS were slightly more favourable than in the GSK PP but did not reach statistical significance, though numbers were small.

Subgroup analyses: *Post hoc* subgroup analyses and modelling were used to identify the two GSK proposed populations. The CS compares two options for eosinophil threshold: ≥150/μL at screening or ≥300/μL in the previous 12 months. Patients with ≥150/μL at screening had a greater reduction in exacerbations for mepolizumab vs. placebo than patients with <150/μL; this was not the case when the population was subgrouped using a threshold of ≥300/μL in the previous 12 months. The company

use this as the basis for focussing on patients with ≥150/μL at screening. In terms of exacerbation history, subgroup analyses in DREAM and MENSA suggested that patients with more previous exacerbations had a greater reduction in exacerbations for mepolizumab vs. placebo, though the findings were not conclusive. Potential issues relating to these sub-populations are discussed in Section 1.3.

Open-label extension studies: The CS provided data on two open-label, non-randomised, non-controlled extension studies enrolling patients completing the pivotal RCTs. Patients in COSMOS (from MENSA and SIRIUS) either continued mepolizumab without interruption or switched from placebo to mepolizumab 100mg SC for 52 weeks. Patients in COLUMBA (from DREAM) had a ≥12--month treatment break and subsequently received mepolizumab100mg SC. COLUMBA is ongoing and patients will receive mepolizumab for up to 3.5 years. The exacerbation rate per year in COLUMBA was 0.67; this was lower than the rate of 1.24 observed in the DREAM mepolizumab ITT group. The rate per year in COSMOS was 0.93; this was similar to the rate of 0.88 observed in the MENSA mepolizumab ITT group but was higher than the rate of 0.68 observed in the SIRIUS trial.

Indirect comparison of mepolizumab vs. omalizumab: The company undertook a network meta-analysis (NMA) of trials comparing mepolizumab or omalizumab to standard of care. The main analysis includes the full ITT populations for both mepolizumab and omalizumab. Secondary analyses used full-trial populations for omalizumab but a subgroup of patients from mepolizumab trials who were also eligible for omalizumab (eosinophilic and allergic asthma). Patients in the omalizumab trials in the main analysis were less severe (≥1 exacerbation in previous year) than in the mepolizumab trials (≥2 exacerbations). The main analysis compared two double-blind mepolizumab RCTs (MENSA and DREAM) with two double-blind omalizumab RCTs (INNOVATE and EXTRA). Two additional open-label RCTs of omalizumab were included in secondary analyses (Niven 2008 and EXALT).

Based on a fixed effects NMA undertaken by the company, mepolizumab gave a reduction in clinically significant exacerbations compared with omalizumab (RR=0.664, 95% credible interval (CrI) 0.513, 0.860). Conversely, mepolizumab was comparable with omalizumab for exacerbations requiring hospitalisation (RR=0.932, 95% CrI 0.350, 2.490) and FEV_1 (RR=0.645, 95% CrI -2.652, 3.959). The company notes that results should be treated with caution since many trial patients were not eligible for both treatments, and study populations differed in severity. Given the heterogeneity between the trials included in the NMA, the ERG considers that the use of a fixed effects model should be interpreted with caution. A random effects NMA undertaken by the company indicates that the reduction in exacerbations is not statistically significant (RR=0.664, 95% CrI 0.283, 1.498). For

exacerbations requiring hospitalisation, the treatment effect non-significantly favours omalizumab in more restricted populations. The CS concludes that it is a reasonable assumption that, in patients who are eligible for both drugs, mepolizumab would be at least as effective as omalizumab.

Safety of mepolizumab: In the RCTs, the risk of eczema, nasal congestion and dyspnoea were potentially higher with mepolizumab than placebo. Adverse events (AEs) of special interest were: systemic, hypersensitivity and injection site reactions; cardiac events; infections, and; malignancies. Infusion-related reactions were higher for IV (but not SC) mepolizumab than placebo whilst injection site reactions were higher for SC (but not IV) mepolizumab (8%) than placebo (3%). Hypersensitivity reactions, infections and malignancies occurred at similar rates for mepolizumab and placebo and there were no reports of anaphylaxis. Rates of all cardiac events were similar for mepolizumab and placebo, whilst rates of serious cardiac events were slightly higher for mepolizumab, though numbers were small. The incidence of the following serious adverse events (SAEs) was higher for mepolizumab than placebo: herpes zoster (2 vs. none); hypertension (2 vs. none); and myocardial ischaemia (2 vs. none). There are few long-term safety data. In the RCTs and open-label studies, 5%-6% of patients on mepolizumab 100mg SC developed anti-mepolizumab antibodies, which the CS states did not discernibly impact upon the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients. Neutralising antibodies were detected in one subject.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

Limitations of the trials: Patients were excluded from SIRIUS if they were unable to achieve a stable dose of OCS, which may not reflect clinical practice. Trial durations were relatively short (24 to 52 weeks). The primary outcome in DREAM and MENSA (clinically significant exacerbations) is a composite outcome including the requirement for systemic OCS (or double maintenance dose) and/or hospitalisation and/or ED visits.

Statistical justification for the sub-populations: The ERG considers that the *post hoc* subgroup and modelling analyses used to justify the GSK proposed populations should be interpreted with caution. Multivariate modelling of DREAM data showed that patients with a blood eosinophil count ≥150 cells/μL at screening had a ≥30% reduction in rate of exacerbations for mepolizumab vs. placebo; however, the uncertainty associated with the predicted rate reduction is not clear. The blood eosinophil threshold giving a 30% reduction in exacerbations varies between DREAM and MENSA and by number of previous exacerbations. The CS compares two options for a blood eosinophil threshold: ≥150/μL at screening or ≥300/μL in the previous 12 months. However, the results observed using a threshold of ≥300/μL in the previous 12 months (indicative of more severe asthma) were not intuitive and raise concerns over potential confounding factors.

Clinical validity of sub-populations: The CS states that the thresholds for eosinophil level and previous exacerbations were clinically plausible and practical to implement according to severe asthma specialists. In terms of eosinophil level, the European Medicines Agency (EMA) concluded that eosinophil levels were not sufficiently predictive to justify a specific cut-off within their marketing authorisation. Clinical advisors to the ERG advised that a threshold of ≥300 cells/μL in the previous 12 months would be more appropriate than ≥150/μL at screening, firstly because 150/μL is within the normal range and secondly because eosinophil levels can fluctuate. Clinical advisors to the ERG considered that a threshold of ≥4 previous exacerbations was clinically appropriate, and was consistent with NICE guidance for omalizumab which restricts the use of the drug to people requiring continuous or frequent treatment with oral corticosteroids (≥4 courses in the previous year).

Evaluation of the indirect comparison: The indirect comparison methods appear broadly appropriate. However, the ERG considers that the results of the random effects model provide a more appropriate (and more conservative) estimate than those of the fixed effects model given the heterogeneity between trials. The company also acknowledges that the results should be treated with caution since only a small proportion of patients in the mepolizumab and omalizumab trials were eligible for both treatments, and study populations differed in terms of severity.

1.4 Summary of cost effectiveness evidence submitted by the manufacturer

The manufacturer supplied a *de novo* cohort Markov model constructed in Microsoft Excel©. The perspective used was that of the NHS in England. The cycle length was set to four weeks and a lifetime time horizon (approximately 92 years) was used. A discount rate of 3.5% per annum was used both for costs and utilities. The model includes four states: (i) on-treatment before continuation assessment; (ii) on-treatment after continuation assessment; (iii) off-treatment and; (iv) death. All patients on a biologic treatment enter the model in the 'on-treatment before continuation assessment' state, until the continuation assessment. After continuation assessment, patients transition either to 'on-treatment after continuation assessment' or 'off-treatment' depending on whether or not they meet a continuation criteria: patients on mepolizumab continued on treatment unless the exacerbation rate worsened compared with the previous year whilst patients on omalizumab continued only if they achieved a physician-rated global evaluation of treatment effectiveness score of good or excellent. Patients in the 'on-treatment after continuation assessment' state transition to the 'off-treatment' state when they discontinue treatment. All patients on SoC enter the model in the 'off-treatment' state. During any cycle, patients can transition from any of the alive states to death as a consequence of either asthma-related mortality following an exacerbation or due to other causes.

The main comparison considered by the company is SoC. Effectiveness data for the main comparison were derived from a subgroup of the MENSA trial. Given that a proportion of patients of the GSK PP

([redacted]) were also eligible for omalizumab, the company included a comparison of mepolizumab with omalizumab. The company conducted a NMA to compare the effectiveness of mepolizumab and omalizumab.

The cost of mepolizumab used in the model included the Patient Access Scheme (PAS) proposed by the company. The list price reported in the BNF was used for omalizumab, as directed by NICE, although a commercial-in-confidence PAS is in place. Unit costs were taken from the PSSRU, BNF, and NHS Reference Costs.

All analyses in the CS used the PAS for mepolizumab. In their base case analysis, the company estimates that the probabilistic incremental cost-effectiveness ratio (ICER) for mepolizumab versus SoC is £19,511 per quality-adjusted life year (QALY) gained ([redacted] QALYs gained at a cost of [redacted]) in the GSK PP, and £15,478 per QALY gained ([redacted] QALYs gained at a cost of [redacted]) in the GSK PP excl. stable mOCS. Based on the list price for omalizumab, the company's analysis estimates that mepolizumab dominates omalizumab as it is estimated to be less expensive and more effective. One way sensitivity analyses undertaken by the company, where the mean values were replaced with values from the relevant 95% confidence intervals, show that the ICER is most sensitive to the assumed utility values and the assumed exacerbation RRs for mepolizumab and SoC. Scenario analyses undertaken by the company show that the source of the asthma related mortality rates has the biggest impact on the ICER, followed by amending the assumed age at baseline and the source of the utilities. In the comparison of mepolizumab with omalizumab, the percentage of omalizumab responders and the source of the omalizumab treatment cost had the biggest impact on the ICER.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG has concerns regarding the threshold of blood eosinophil count of ≥150 cells/μL at screening included as a requirement in the GSK PP because it was unclear whether this would impact upon the effectiveness of mepolizumab in the medium- and long-term, especially since a blood eosinophil count of ≥300 cells/μL in the previous year would by definition be greater than ≥150 cells/μL at some point in the previous year.

The ERG notes that the standard of care against which mepolizumab is compared should include mOCS, given that the GSK PP excl. stable mOCS group had suffered four or more exacerbations in the previous year, a sign of poorly controlled asthma at Step 4, and that Step 5 treatment usually includes the use of mOCS. The addition of mOCS in patients who are not contraindicated would likely reduce the average number of exacerbations and therefore reduce the relative benefit of mepolizumab. The SIRIUS trial could have provided a better insight for this comparison, but the analysis using the data from SIRIUS was subject to a high degree of uncertainty due to the small size of the GSK PP in this trial.

The ERG has concerns regarding the continuation criteria defined for mepolizumab. Grammatically this should be a continuation criterion but we have used continuation criteria to be consistent with the CS. According to these, all patients who did not experience a worsening in exacerbation rates would to receive mepolizumab. This implies that a proportion of patients would remain on mepolizumab despite experiencing no improvement. The ERG also has concerns regarding the calculation of exacerbation rates for patients meeting the continuation criteria: these rates were measured in the MENSA trial shortly after the beginning of treatment, based on a 16-week time span and therefore might not be representative of the long-term effectiveness of mepolizumab and may be affected by seasonality. Furthermore, there may be a regression to the mean.

Regarding the comparison with omalizumab, the ERG notes the importance of the decision taken by the company to use the cost of omalizumab as calculated through a study; this results in an estimated drug cost which was more than 40% higher than that reported within the assessment report of the omalizumab MTA.

For these reasons, the ERG believes that there is considerable uncertainty regarding the true cost-effectiveness of mepolizumab add-on treatment compared to standard of care and omalizumab.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

Clinical trial data were presented for the ITT population and the GSK proposed populations across a range of relevant clinical outcomes. Data were meta-analysed across trials. Whilst there were gaps in the data provided in the CS, more complete data were provided in the clarification response.

The model used appears conceptually appropriate with only a few minor implementation errors. It contained the functionality to assess the impact of changing parameters and relevant structural uncertainties on the ICER. A number of built-in alternative scenarios were included.

1.6.2 Weaknesses and areas of uncertainty

The ERG considers that the *post hoc* analyses used to justify the GSK proposed populations should be interpreted with caution, particularly the eosinophil threshold of ≥150 cells/μL at screening. The results of the NMA should also be interpreted with caution, given the heterogeneity between the trials and the fact that only a subset of the trial patients was eligible for both mepolizumab and omalizumab.

The cost-effectiveness results are sensitive to the utility values used in the model and the methods used to model asthma-related mortality. Alternative methods of calculating exacerbation rates for patients meeting the continuation criteria also have a major impact on the ICER.

Both the company and clinicians consulted by the ERG claim a high disutility caused by the side effects of long-term use of OCS, however the scenario analysis undertaken by the company estimates only a very small benefit. The CS states that 'An OCS dose reduction and discontinuation approach were explored but the scenario analyses did not generate the expected upside of sparing patients from OCS.' GSK further states that the results presented in the CS 'are in contrast to those from the approach taken in the NICE omalizumab MTA which showed an improvement [in the ICER] by £4,000-£6,000/QALY gained and £10,000 - £17,000 /QALY gained'. Thus, the true benefits of OCS sparing appear uncertain. However, it is noted that the cessation of OCS use was greater for omalizumab than for mepolizumab, as 41.9% of patients discontinued mOCS on omalizumab compared with 14.5% on mepolizumab.

The key uncertainty in the clinical evidence base for mepolizumab versus omalizumab concerns the absence of head-to-head RCTs comparing these drugs. A key uncertainty in the cost-effectiveness modelling is the cost of the omalizumab treatment, which depends on the weight and IgE levels of a patient, and the estimate for the cost of omalizumab used in the company's model is markedly higher than that used in the previous NICE appraisal of omalizumab. In addition, some of the scenario analyses exploring the comparison between omalizumab and mepolizumab resulted in ICERs substantially different to that of the base case.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The probabilistic base case ICERs presented in the CS comparing mepolizumab with SoC were £19,511 and £15,478 per QALY gained for the GSK PP and GSK PP excl. mOCS, respectively. The ERG made five changes to the company's base case. These included: (i) using directly measured EQ-5D scores instead of the scores mapped from SGRQ; (ii) using the asthma-related mortality rates estimated by the company combining the data from Watson *et al.*[1] and Roberts *et al.*[2]; (iii) removing the use of a fixed duration stopping rule for mepolizumab treatment; (iv) calculating the QALY loss due to exacerbations using the average duration of exacerbations observed in MENSA and; (v) setting the exacerbation rates for those meeting the continuation criteria equal to those derived from the COSMOS study. When taken in isolation, each of these changes led to an increase in the ICER, the largest of which was attributable to the modelling of asthma-related mortality. The combined effect of these changes increases the probabilistic ICER from £19,511 per QALY gained to £35,440 per QALY gained ([redacted] QALYs gained at a cost of [redacted]) in the GSK PP, and from £15,478 per QALY gained to £33,520 per QALY gained ([redacted] QALYs gained at a cost of [redacted]) in the GSK PP

excl. stable mOCS. The ERG notes that using data from the ITT population with ≥4 exacerbations, rather than with an additional criterion of having ≥150 cells/μL at screening, would produce a more plausible ICER for mepolizumab versus SoC. However, the ERG did not have the data required to undertake this analysis.

For the comparison of mepolizumab versus omalizumab, the base case analysis presented in the CS, which does not incorporate the omalizumab PAS, concludes that mepolizumab dominates omalizumab. The ERG applied three alternative assumptions: (i) the cost of omalizumab (without the PAS) was based on that used within the previous NICE appraisal of omalizumab; (ii) the exacerbation RRs were based on a mOCS population, and; (iii) a random effects NMA model was applied. On the basis of this exploratory analysis, the ICER for omalizumab versus mepolizumab was approximately £43,000 per QALY gained. An estimate of the cost-effectiveness of mepolizumab compared to omalizumab when the omalizumab PAS is assumed is provided in a confidential appendix.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The Evidence Review Group (ERG) considers the company's description of the underlying health problem in the company submission (CS) to be largely appropriate, up to date and relevant to the decision problem in the final NICE scope. However, a detailed exploration of how eosinophilic asthma is defined and diagnosed was lacking. The ERG provides a description below.

Asthma, severe asthma and severe refractory asthma: Asthma is a broad condition characterised by inflammation of the airways leading to reversible (and in some cases, irreversible[3]) airway obstruction. Asthma symptoms include wheezing, chest tightness, cough and shortness of breath, and exacerbations (worsening) of symptoms can lead to hospitalisations and death. Asthma varies in its severity, but in most cases can be controlled with a combination of medications, which in the UK are administered in a step-wise manner (steps 1 to 5, 1 being the lowest step) until control is reached, according to the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidelines.[4] The level of treatment required is also a measure of the severity of the condition. There were 1,242 deaths from asthma in the UK in 2012. It is estimated that approximately 5.4 million people in England and Wales currently receive treatment for asthma.[5]

The American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force defines severe asthma as *''asthma that requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming 'uncontrolled' or that remains 'uncontrolled' despite this therapy.''*[6] These patients suffer from frequent exacerbations, despite controller medications, and have a decreased quality of life due to uncontrolled symptoms and treatment side effects, as many take oral corticosteroids long-term. The impact of exacerbations on patients varies, with some being managed adequately at home with oral corticosteroids, but others requiring systemic corticosteroids and a hospital stay; in addition some patients die from an asthma exacerbation. The CS states that 5% of patients remain uncontrolled despite treatment (CS p25), though this proportion is variably reported in the literature, with a range of (at least) between 5 and 10%.[7, 8]

The term "severe refractory asthma" is used in the licence and the summary of product characteristics (SmPC) for mepolizumab.[9] According to definitions from the ATS/ERS[6] and the BTS/SIGN guidelines,[4] these are patients who remain uncontrolled despite treatment with high dose ICS plus a second controller and/or systemic corticosteroids. In addition, the BTS/SIGN guidelines and the National Health Service (NHS) England A14 Service Specification for Severe Asthma,[10] state patients should also have undergone assessment for other explanations, management of co-morbidities, and

assessment for adherence to therapy before being termed refractory. The criteria relating to compliance was emphasised in the National Institute for Health and Care Excellence (NICE) guidance for omalizumab.[11]

Severe eosinophilic asthma: Eosinophilic asthma is a distinct phenotype of asthma characterised by tissue and sputum eosinophilia, a thickening of the basement membrane and, often, responsiveness to corticosteroids.[8] It can be present in mild, moderate or severe asthma.[8] It is, however, associated with more severe disease, late onset, atopy and steroid refractoriness. The diagnosis of eosinophilic asthma is problematic in clinical practice. Induced sputum eosinophil levels of 1-3%[8] are commonly interpreted as indicating eosinophilic disease, however, this test is impracticable in routine care. Alternatives include peripheral blood eosinophil counts, fractional exhaled nitric oxide (FeNO), serum immunoglobulin E (IgE), and periostin levels. However, a recent US review[8] reported that these have limited diagnostic accuracy: levels of blood eosinophils >300 cells/μL had a positive predictive value of only 50% in identifying an eosinophilic asthma phenotype (defined as sputum eosinophils of >2%), serum IgE had no correlation with eosinophilia,[12] studies relating to FeNO appeared inconsistent,[13-15] and the diagnostic utility of periostin was promising but is as yet undetermined. Further, a systematic review and meta-analysis of tests for eosinophilia found sensitivities and specificities of 0·66 (95% Confidence Interval (CI) 0·57–0·75) and 0·76 (95% CI 0·65–0·85) for FeNO; 0·71 (95% CI 0·65–0·76) and 0·77 (95% CI 0·70–0·83) for blood eosinophils; and 0·64 (95% CI 0·42–0·81) and 0·71 (95% CI 0·42–0·89) for IgE respectively.[16] One study concluded that thresholds for interpreting blood eosinophils varied greatly.[17] A Dutch study reported blood eosinophil cut-offs from a derivation and validation cohort, and concluded that the best diagnostic accuracy (for identifying sputum eosinophils >3%) was achievable at values of approximately 220 cells/μL for the derivation cohort, though diagnostic accuracy was reduced in the validation cohort.[18]

Despite only moderate diagnostic accuracy being reported for blood eosinophils in the literature, the test is used in clinical practice to monitor disease.[4] There is no national or international consensus on how to interpret such tests; however, clinical advisors to the ERG stated that a level of ≥300 cells/μL in the previous 12 months is a commonly used cut-off. The CS states *"Eosinophilic asthma inflammation can be measured in both blood and sputum, but recent studies have confirmed that late-onset severe refractory eosinophilic asthma can be reliably characterised by establishing blood eosinophil thresholds in the presence of high-dose ICS in a poorly controlled exacerbating phenotype"* (p 25-26), and references two articles[19, 20] to support this statement, both of which are re-analyses of the phase IIb trial, "Dose Ranging Efficacy And safety with Mepolizumab in severe asthma" (DREAM), which forms part of this submission. The ERG concludes that the use of blood eosinophilia to identify eosinophilic asthmatics appears to be a clinically relevant approach, but that the criteria that should be used to diagnose eosinophilic disease are unclear and of uncertain accuracy.

Impact on patients, carers and society: The company use an Asthma UK report, Fighting for Breath,[21] as the main source of information about how asthma impacts on the lives of patients and carers. This is a report of qualitative interviews with asthma sufferers and carers summarising the impact on patients, outlining the impact on quality of life of daily symptoms of breathlessness, the impact of sudden severe attacks, and the difficulty some patients have in maintaining full time employment. Further published journal articles may have been useful to support this source.

Asthma-related mortality: The company refer to the National Report for Asthma Deaths (NRAD) for data on asthma-related mortality.[22] Severe asthmatics were found to account for 39% of deaths from asthma, and the company argues that as severe asthmatics are only a small proportion of the total asthma population (5-10%), mortality is still *"an issue"* for this population. The CS states that the definition of severe asthma used in the NRAD report was *"those who were prescribed four asthma medications and those who had been admitted to hospital in the past year, needed OCS daily or had two or more prescriptions for systemic corticosteroids in the past year"* (CS p 28). However, in the NRAD report it is stated that patients at Step 4 or 5 of the BTS/SIGN guidelines[4] were also classed as severe.

2.2 Critique of manufacturer's overview of current service provision

The company's overview of current service provision is mostly appropriate and relevant to the decision problem in the final NICE scope.

BTS/SIGN guidelines: The company identified the BTS/SIGN guidelines[4] for the diagnosis and management of asthma as the most relevant clinical guideline, in addition to the NICE guidance relating to omalizumab. The BTS/SIGN guidelines describe a step-wise approach to management, whereby treatment doses are increased and other controller medications are added when control is poor. Treatment should be stepped down when control is good, though it is widely acknowledged that this does not always happen in practice, and a number of patients may remain on a step that is higher than necessary. There are five steps in the guidelines. These are:

- Step 1 (mild intermittent asthma): Inhaled short-acting beta-2 agonist as required.
- Step 2 (regular preventer therapy): Add inhaled corticosteroid (200–800µg per day).
- Step 3 (initial add-on therapy): Add an inhaled long-acting beta-2 agonist. If control remains inadequate, increase the dose of the inhaled corticosteroid to 800µg per day. If there is no response to the inhaled long-acting beta-2 agonist, stop this drug and increasing the inhaled corticosteroid dose 800µg per day. If control is still inadequate, try a leukotriene receptor antagonist or slow-release theophylline.

- Step 4 (persistent poor control): Consider increasing the dose of inhaled corticosteroid up to 2000 µg per day. Consider adding a fourth drug (for example, a leukotriene receptor antagonist, slow-release theophylline or a beta-2 agonist tablet).
- Step 5 (continuous or frequent use of oral steroids): Use daily steroid tablets at the lowest dose providing adequate control. Maintain high-dose inhaled corticosteroid at 2,000µg per day. Consider other treatments to minimise the use of steroid tablets. Refer patients to specialist care.

In the clinical care section of the CS (Section 3.3 p27), the company identifies patients at BTS/SIGN[4] Step 5 as the focus of the appraisal, although p11 of the CS states that *"people with severe refractory asthma are typically termed Step 4 or Step 5 patients"*. However, the NICE scope considers the relevant comparators to be care according to Step 4 or Step 5 of the BTS/SIGN guidelines.[4] This corresponds to the steps that would fall within the ATS/ERS definition of severe asthma provided in Section 2.1, and is consistent with the definition used in the NRAD report (p31).[22] As such, the ERG believes that the company's focus is too narrow and that both Steps 4 and 5 should be considered to be relevant.

NHS England Service Specification: As well as the BTS/SIGN guidelines, the company cites the NHS England A14 Service Specification for Severe Asthma[10] as a relevant source of information about how severe asthma patients would be cared for. The company does not provide much detail about this service specification, and the ERG provides an overview here.

The service specification describes tertiary-level specialist centres where patients would receive a multidisciplinary assessment that: assesses and treats co-morbidities such as sleep apnoea and gastroesophageal reflux disease; identifies and removes triggers; eliminates other conditions that mimic asthma; improves adherence and compliance to existing treatments; treats and prevents complications of long-term OCS use; provides patient and healthcare professionals education; quantifies asthma phenotype; measures airway inflammation; and prescribes novel biologics to the correct groups. Notably, the service specification includes the measurement of sputum eosinophilia, and full blood count, which would include blood eosinophilia levels. The assessment would involve a consultant respiratory physician, physiotherapist, asthma nurse specialist, health psychologist, dietician and allergist and would be conducted over two days. These centres are intended to act as *"an advisory lead on omalizumab and other high cost novel biological therapies for the region they serve. The decision to treat and the initial assessment of efficacy will occur at the specialist centres… the drug may be delivered locally in the longer term. The specialist centre will continue to oversee… via outpatient review every 6 months."*[10]

As such, the statement in the CS that "*In England this usually takes place at a tertiary care centre … We believe mepolizumab will fit into the existing care pathway for severe asthma"* is considered by the ERG to be reasonable. It is also correct that eosinophilia will have been tested for and so will not require any additional testing. Measurement of sputum eosinophilia levels may present an alternative, more accurate, method for the identification of eosinophilic patients than using blood eosinophilia levels, however only a limited number of centres have access to sputum eosinophilia testing.

Omalizumab: The NICE guidance for omalizumab (Xolair, an anti-IgE monoclonal antibody) states:

"Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older:

- *who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year),* ***and***
- *only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme.*[11, 23]

Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta2 agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate."

The company correctly state that only a proportion of patients who are eligible for mepolizumab will also be eligible for omalizumab, the main difference being that omalizumab is restricted to patients with confirmed IgE-mediated disease who have had ≥4 steroid-treated exacerbations in the previous year. The company used data from an unpublished non-drug interventional study (Identification and Description of Severe Asthma Patients in a Cross-sectional Study; IDEAL) to estimate the proportion of severe patients who have eosinophilic disease in the UK and Wales and estimated this to be approximately [redacted]. Of these patients, the company estimate (from the same data) that [redacted] would be eligible for omalizumab. As described above, omalizumab is only available through specialist referral to a tertiary centre for assessment.

3 CRITIQUE OF THE COMPANY'S DEFINITION OF DECISION PROBLEM

The NICE scope and the company's interpretation of the decision problem are described in the CS (p17-18). This is reproduced here as Table 1.

3.1 Population

3.1.1 NICE scope and European Medicines Agency (EMA) licence

The population described in the NICE final scope is *"Adults with severe eosinophilic asthma"*, though the licence is for *"severe refractory eosinophilic asthma"*. The population is not defined in any detail within the NICE scope or the BTS/SIGN guidelines.[4] There are three components to the definition given in the licence: "severe", "refractory" and "eosinophilic."

Severe asthma is defined as *''asthma that requires treatment with high dose ICS plus a second controller and/or systemic corticosteroids to prevent it from becoming 'uncontrolled' or that remains 'uncontrolled' despite this therapy"* (p343) in the ATS/ERS guidelines.[6]

Refractory asthma is the latter set of patients who remain uncontrolled despite such treatment (see Section 2.1). The ERG assumes that as the licence for mepolizumab stipulates "refractory" patients, this group should form the focus of the assessment. According to BTS/SIGN guidelines,[4] patients should be assessed for compliance and other causes before being diagnosed as refractory. Compliance is an important issue to address as where improved compliance leads to improved control, the use of additional expensive drugs would be inappropriate. This issue may be a consideration for guidance, as it featured in the guidance issued for omalizumab.[11]

Eosinophilic asthma is characterised by tissue and sputum eosinophilia (see Section 2.1). However, there is no specific definition for the level of eosinophilia that is considered "eosinophilic." Sputum eosinophil levels of 1-3% are commonly interpreted as indicating eosinophilic disease.[8] Blood eosinophil counts are used in clinical practice[4] but there is no national or international consensus regarding which cut-off indicates eosinophilic disease. However, clinical advisors to the ERG stated that ≥300 cells/μL in the previous 12 months is a commonly used cut-off in clinical practice.

3.1.2 GlaxoSmithKline (GSK) clinical trial evidence (ITT population)

Broadly, the intention to treat (ITT) populations in the pivotal trials are consistent with the populations in the scope, since the trials aimed to recruit patients with severe eosinophilic asthma. However, the degree of severity and degree of eosinophilia are not clearly specified in the final NICE

scope. The CS therefore provides data for the ITT trial populations and also for sub-populations of patients meeting higher thresholds for severity and eosinophil count (Section 3.1.3).

The three pivotal trials are as follows: DREAM (Pavord *et al*., 2012[19]), "Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma" (MENSA, Ortega *et al*., 2014[24]) and "Steroid Reduction with Mepolizumab Study" (SIRIUS, Bel *et al*., 2014[25]). The pivotal trials include patients requiring high-dose ICS plus additional controllers, with or without maintenance oral corticosteroids (mOCS) (DREAM and MENSA) or requiring mOCS (SIRIUS), and as such include severe asthma patients. SIRIUS includes patients on mOCS, which represents a more severe spectrum of patients than DREAM and MENSA. Two of the trials (DREAM and MENSA) also use a criterion of ≥2 asthma exacerbations requiring treatment with systemic corticosteroids in the previous 12 months, which is presumably a measure of loss of control. It is unclear if patients had been assessed for compliance and other causes, which should be done before diagnosing refractory disease. The criterion of ≥2 exacerbations in the previous year is not mentioned for SIRIUS, possibly because these patients are receiving mOCS which may reduce exacerbation frequency.

Forced expiratory volume in 1 second (FEV_1) <80% was a selection criterion for all three mepolizumab trials. However, the clinical advisors to the ERG noted that patients can have multiple exacerbations whilst having an FEV_1 of 80% or greater. As such, patients with FEV_1>80% are missing from the clinical evidence submitted by the company.

Eosinophilic asthmatics are usually defined as those with sputum eosinophils greater than 1-3%,[8] though as this test is difficult to perform in routine practice and is often not used. There is a lack of agreement about what surrogate markers can be used in clinical practice, and at what cut-off patients should be considered to be eosinophilic (see Section 2.1). The licence does not specify an eosinophil cut-off. The trials included in the CS have identified eosinophilic patients using various methods. MENSA and SIRIUS included patients with either blood eosinophils ≥150 cells/μL at screening or eosinophils ≥300 cells/μL in the past 12 months, whilst the earlier DREAM trial included patients with any of four criteria (blood eosinophils ≥300 cells/μL *or* sputum eosinophils ≥3% *or* exhaled nitric oxide (FeNO) ≥50 ppb *or* prompt deterioration of asthma control following ≤25% reduction in inhaled or oral corticosteroid dose in previous 12 months). The company provided data for the ITT population as well as for a more severe population based on eosinophil count and history of exacerbations (see below).

All trials included a small number of patients who were younger than 18 years of age. All trials list a number of exclusions, including current and former smokers, those with concurrent respiratory

disease and those with other comorbidities (e.g. malignancy, liver disease). Data are therefore limited in these groups.

3.1.3 GSK Proposed Populations

In addition to the ITT populations, the CS focusses on two "GSK proposed populations" consisting of sub-populations of patients from all three trials, and which the CS states are *"a more severe population within the anticipated licence with increased disease burden and an enhanced potential for clinical benefit and a more cost effective use of NHS resources"* (CS p75). The ITT population, the two GSK proposed populations, and a further sub-population requested by the ERG, are defined below. For brevity within the report the ERG has renamed the non-ITT populations put forward by the company as "GSK PP" and "GSK PP excl. stable mOCS", whilst the further sub-population requested by the ERG is referred to as "stable mOCS", as indicated in the parentheses alongside the descriptions below. The ERG notes that the term "stable" in relation to mOCS is used for ease of reading and refers to having fewer than four exacerbations in the previous year. The relevant sub-populations are defined as follows:

- **Intention-to-treat (ITT) population:** All trial patients who were randomised and received at least one dose of study medication; this is actually a form of modified ITT (mITT) but this population is referred to in the ERG report as the ITT population for consistency with the CS.
- **GSK proposed population (GSK PP):** Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/µl at initiation of treatment; and ≥4 exacerbations in the previous year and/or dependency on mOCS (regardless of exacerbations in previous year).
- **GSK PP excluding mOCS users with <4 exacerbations (GSK PP excl. stable mOCS):** Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/µl at initiation of treatment; and ≥4 exacerbations in the previous year.

The ERG also requested data on the following population, which constitutes the patients in the GSK PP who are not within the GSK PP excl. stable mOCS:

- **mOCS users with <4 exacerbations (stable mOCS):** Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/µl at initiation of treatment and dependency on mOCS but <4 exacerbations in the previous year.

The company's rationale for the GSK PP is based on a set of *post hoc* modelling analyses and subgroup analyses of DREAM and MENSA, described further in Section 4.2.4.2. Briefly, subgroup analyses of both DREAM and MENSA showed that the reduction in exacerbations for mepolizumab

vs. placebo was greater for patients with higher baseline blood eosinophils than for those with lower baseline eosinophils. In addition, the reduction in exacerbations was greater for patients with more previous exacerbations than those with fewer previous exacerbations in DREAM and MENSA. In addition, the company proposes that mOCS users meeting the eosinophil cut-off should be included in this population (even if they had fewer than 4 exacerbations in the past year) since mOCS users are likely to be a severe group and there are documented clinical benefits associated with reducing the use of mOCS.

The company's rationale for also presenting data for the "GSK PP excl. stable mOCS" population is that this population (excluding mOCS users with <4 previous exacerbations) may show greater effectiveness and cost-effectiveness, since the use of corticosteroids may already have reduced exacerbations in mOCS users, therefore there may be less potential to demonstrate a further reduction in exacerbations in these patients. The CS states that the primary objective in mOCS users would be to reduce steroid exposure whilst maintaining asthma control, but that it is challenging to fully capture the benefits of reducing steroid exposure in the clinical and cost-effectiveness analysis.

Clinical validity and feasibility of GSK PP: The CS (p80) states that, based on modelling and subgroup analyses, patients with ≥150 cells/µl baseline blood eosinophils at screening and ≥4 exacerbations in the 12 months prior to screening experienced the most benefit from therapy with add-on mepolizumab, and that *"the clinical viability of this conclusion was supported by independent severe asthma specialists' interpretation of the results."* The CS also states that *"clinical experts agree that this population is plausible and practical to implement in practice"* (CS p12). The statistical validity of the modelling and subgroup analyses is discussed in Section 4.2.4.2.

In terms of previous exacerbations, clinical advisors to the ERG considered that a threshold of ≥4 previous exacerbations was clinically appropriate. The CS also notes (p81) that the GSK PP is consistent with current NICE guidance for omalizumab which restricts use to people requiring continuous or frequent treatment with oral corticosteroids (≥4 courses in the previous year). Previous exacerbations (in the GSK PP and the subgroup analyses) are defined in the clarification response (additional clinical question b) as exacerbations requiring systemic corticosteroids (or for subjects on mOCS, a two-fold or greater dose increase). It should be noted that this is different to the definition of clinically significant exacerbations as an outcome in the pivotal trials of mepolizumab, which includes exacerbations requiring systemic corticosteroids and/or hospitalisations or ED visits. Although predictive modelling reported in the CS appears to show a correlation between previous exacerbations and reductions in exacerbation rate relative to placebo, this pattern is less clear from the subgroup analyses (Section 4.2.4.2).

In terms of eosinophil level, the CS notes (p81) that the EMA concluded that eosinophil levels were not sufficiently predictive to justify a specific cut-off level within their marketing authorisation. However, the company states that they *"believe the correlation is sufficient to justify use in identifying a target population with enhanced benefit to be considered for NICE guidance when both cost and clinical effectiveness are criteria for decision making"*. Subgroup analyses indicate that a blood eosinophil threshold of ≥150/μL at screening provides a greater reduction in exacerbation rate than a threshold of ≥300/μL in the previous 12 months. However, it is not clear why this should be the case. Clinical advisors to the ERG advised that a blood eosinophil threshold of 300/μL in the previous 12 months would appear more appropriate than 150/μL at screening, because 150 cells/μL was a relatively low count within the normal range, and because eosinophil levels can fluctuate.

3.2 Intervention

The intervention in the CS is consistent with the final NICE scope. The technology is mepolizumab (brand name Nucala®), a humanised anti-interleukin 5 (IL5) monoclonal antibody (IgG1, kappa). Mepolizumab is indicated as an add-on treatment for severe refractory eosinophilic asthma in adult patients.[26] The licensed dose is 100mg administered subcutaneously (SC) every 4 weeks with the company assuming that this will be undertaken by a specialist asthma nurse. A dose of 75mg administered intravenously (IV) every 4 weeks is used in some of the pivotal trials. Data for the 75mg intravenous (IV) dose are also included in the CS and the ERG report, since it is stated in the CS and in the summary European Public Assessment Report (EPAR) for mepolizumab[27] that the 100mg SC and 75mg IV doses show bioequivalence.

3.3 Comparators

The comparators in the CS are consistent with the NICE scope. The pivotal trials compare best standard care plus mepolizumab vs. best standard care plus placebo. For people with severe persistent allergic IgE-mediated eosinophilic asthma, the company has undertaken an indirect comparison of mepolizumab vs. omalizumab (Xolair®, an anti-IgE monoclonal antibody indicated for allergic IgE-mediated asthma).

3.4 Outcomes

The outcomes in the CS are consistent with the NICE scope. These include clinically significant exacerbations, exacerbations requiring hospitalisation or hospitalisation and/or ED visits, use of maintenance oral corticosteroids (mOCS), lung function, health-related quality of life (HRQoL), AEs, and cost-effectiveness in terms of the incremental cost per quality-adjusted life year (QALY) gained.

3.5 Other relevant factors

The company raised an equity issue within their submission. The CS states that there is a *"possible risk of the Committee issuing guidance which may not be deemed equitable across the eligible patient population."* The argument for this in the CS is that patients on mOCS *"will appear less cost-effective compared to the GSK proposed population when excluding mOCS users who did not achieve the required 4 exacerbations in the previous year, despite representing a more severe population. Thus, to ensure this equitability issue is addressed both populations (GSK proposed population and GSK proposed population excluding mOCS users with < 4 exacerbation in the previous year) are presented in the clinical and cost effectiveness section"*.

The ERG notes that this concern is also related to whether the use of mOCS should be a comparator to mepolizumab for patients not on mOCS who have four or more exacerbations in the previous year. Clinical advisors to the ERG expressed concerns regarding the use of mOCS in this group due to the side effects of OCS, but commented that patients who are uncontrolled would either take prednisolone during exacerbations or receive low-dose mOCS if the exacerbations become very frequent. Furthermore, clinical advisors to the ERG highlighted that if a positive recommendation was provided for those patients not on mOCS but not for those patients on mOCS, then there could be an incentive for clinicians to remove mOCS, allowing a patient to become uncontrolled and to subsequently meet the criteria for mepolizumab use.

A Patient Access Scheme is in place for mepolizumab. This represents a commercial-in-confidence reduction in the list price from [redacted] per 100mg vial to [redacted] per 100mg vial.

Table 1: The decision problem addressed by the submission (reproduced from CS Table 3)

	Final scope issued by NICE	**Decision problem addressed in the company submission** (all references relate to the company submission)	**Rationale if different from the final NICE scope**
Population	Adults with severe eosinophilic asthma	Evidence is presented for the anticipated licensed population for mepolizumab. We demonstrate the clinical and cost-effectiveness of mepolizumab in a more severe patient population. We seek guidance in the following population: *Adults with severe refractory eosinophilic asthma with a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or dependency on mOCS.*	Mindful of NHS resources and current NHS implementation of NICE guidance for another biologic in severe asthma (omalizumab) guidance is sought in a more severe sub-population of the anticipated licensed indication. This sub-group provides enhanced clinical benefit whilst maintaining a cost-effective proposition for the NHS.
Intervention	Mepolizumab (in addition to best standard care)	Consistent with Final Scope	N/A
Comparator (s)	• Best standard care without mepolizumab For people with severe persistent allergic IgE-mediated eosinophilic asthma: • Omalizumab	Consistent with Final Scope	N/A
Outcomes	The outcome measures to be considered include: • asthma control • incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation • use of OCS • patient and clinician evaluation of response • lung function • mortality • time to discontinuation • adverse effects of treatment • health-related quality of life.	Consistent with Final Scope (Sections refer to CS). • asthma control (Section 4.7) • incidence of clinically significant exacerbations, including those which require unscheduled contact with healthcare professionals or hospitalisation (Section 4.7) • use of OCS (Section 4.7) • patient and clinician evaluation of response (Section 4.7 and Appendix 8.6) • lung function(Section 4.7) • mortality (Section 4.12, 4.13 and 5.3.6) • time to discontinuation (withdrawals are described Section 4.5 and 4.12) • adverse effects of treatment(Section 4.12) • health-related quality of life (Section 4.7)	N/A
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per	Consistent with the Final Scope. • A PAS has been submitted to DH/PASLU (see Section 2).	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission (all references relate to the company submission)	Rationale if different from the final NICE scope
	quality-adjusted life year (QALY), the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	• Costs are considered from an NHS perspective. • A PSS perspective is considered in the narrative.	
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • People who do not adhere to treatment • People who have severe allergic IgE-mediated eosinophilic asthma • People who require maintenance oral corticosteroid treatment • People who require frequent oral corticosteroid treatment.	Where evidence is available this has been presented within the submission document. • People who do not adhere to treatment (patients were required to be adherent to optimised SoC in order to be eligible for mepolizumab) • People who have severe allergic IgE-mediated eosinophilic asthma (Section 4.10) • People who require maintenance oral corticosteroid treatment (Section 4.7 and 5.7) • People who require frequent oral corticosteroid treatment (Section 4.7 and 5.7)	N/A
Special considerations including issues related to equity or equality		Consistent with Final Scope. • No equality issues have been identified. • A possible equity issue has been identified (Section 3.7).	• Primary treatment objective for uncontrolled patients at Step 4 who have not commenced mOCS is reduction in exacerbations. This is also true for patients uncontrolled at Step 5 on mOCS. • For patients at Step 5 who are controlled on mOCS, not only is the treatment objective to reduce exacerbation frequency (although potential to do so may be less than patients at Step 4 due to impact of mOCS), clinicians will also be seeking to reduce systemic exposure to OCS while maintaining asthma control. It is unlikely that we can appropriately capture, economically, the true long term benefit of reducing exposure to OCS. • This is important to note to ensure that any guidance fairly reflects all needs of the patient population in question, which may not be fully captured in presented economic evaluation.

CS = company submission; DH = Department of Health; mOCS = maintenance oral corticosteroids; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Clinical Excellence; PAS = patient access scheme; PASLU = Patient Access Scheme Liaison Unit; PSS = personal social services; QALY = quality-adjusted life year

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The CS includes a systematic review of mepolizumab and omalizumab RCTs to provide data relating to the clinical effectiveness and safety of mepolizumab and for the network meta-analysis of mepolizumab vs. omalizumab. The CS also includes a review of observational studies to obtain further efficacy and safety data relating to omalizumab and relating to mOCS.

4.1.1 Searches

The CS reports a systematic review of maintenance treatments for severe asthma. The review corresponds to a broader remit than the decision problem addressed within the CS. The main comparator for mepolizumab is Standard of Care, consisting of high dose ICS and additional maintenance treatment(s) including mOCS.

The clinical effectiveness component of the review includes two search strategies:

A. RCTs for maintenance treatment of severe asthma
B. Observational studies relating to omalizumab and mOCS

In both cases, a multi-file search was conducted on two platforms:

i) ProQuest (simultaneously searching Medline, Medline in Process and Embase)
ii) The Cochrane Library (including CDSR, DARE, CENTRAL and HTA)

For search A, an appropriate selection of conference abstracts, trial registries and other relevant websites were also searched in addition to the database searches listed above. Whilst it is best practice to search databases one at a time, and this allows more detail in the PRISMA reporting, the ERG recognises that some effort has been made to adapt the ProQuest search strategy to optimise its effectiveness across databases, for example including both MeSH (Medline) and Emtree (EMBASE) indexing terms.

Searches are reproduced in full in the CS Appendix 8.2, although the numbers of results retrieved by each search string have not been included. This made it difficult for the ERG to accurately replicate the ProQuest searches on the Ovid platform (through which we purchase access to the same databases) due to the differences in syntax. The ERG notes that a filter has been used to restrict the results to RCTs; however no source is cited. The ERG acknowledges the company's clarification response (question A1) that *"search strings are based on our usual list of search terms/strings for the topics (RCTs, observational, economic, etc.) and crosschecked with the NICE appraisal document of omalizumab especially for comparators/compounds in this indication"*; however the ERG notes that use of validated filters would be preferred where available, with appropriate referencing.

The ERG notes that the company provided five additional data sources as these were deemed unlikely to have been identified through database or abstract searches. This is described in the CS as 'hand searching.' The Cochrane Handbook for Systematic Reviews defines hand searching as a *"manual page-by-page examination of the entire contents of a journal issue or conference proceedings to identify all eligible reports of trials"*.[28] However, the CS does not provide any details of sources searched by hand, or of dates covered.

Broadly, the searches were likely to have been sufficient to identify all relevant studies of mepolizumab and omalizumab for inclusion in the review of clinical effectiveness.

4.1.2 Inclusion criteria

The inclusion criteria for the company's systematic review of effectiveness are summarised in Table 2. The inclusion criteria were broadly appropriate and consistent with the decision problem specified in the final NICE scope. Studies of patients aged ≥12 years were included (plus one study with patients ≥11 years). The final NICE scope restricts to adults (≥18 years), whilst the pivotal trials of mepolizumab included patients ≥12 years but the majority of included patients were ≥18 years. Therefore this inclusion criterion appears broadly appropriate. Appropriate interventions, comparators, outcome measures and study types were included. Time to discontinuation was listed in the final NICE scope but was not reported in the CS, though withdrawal rates were reported in CS p62-65.

Table 2: Inclusion criteria for systematic review of effectiveness and ERG assessment of appropriateness (adapted from CS Table 6)

Topic	Inclusion criteria for systematic review of effectiveness reported in CS	Appropriateness and consistency with Decision Problem and final NICE scope (ERG assessment)
Population	• Age ≥12 years (one study included patients aged ≥11 years) • Severe (or refractory / difficult-to-treat / persistent / treatment-resistant / uncontrolled) asthma • Patients with and without eosinophilic and allergic asthma subtypes were included in review	Broadly consistent: • Age: NICE scope restricts to adults (≥18 years). Pivotal trials of mepolizumab include patients ≥12 years but majority are ≥18 years • Severe asthma: consistent • Asthma type: studies appropriately narrowed down to eosinophilic or allergic asthma when presenting evidence for mepolizumab and omalizumab
Intervention	• Standard of Care with: o Mepolizumab o Omalizumab	Consistent
Comparators	• As above	Comparator arms in included studies were placebo plus Standard of Care which is consistent
Outcomes	• Efficacy (exacerbations, lung function, asthma control, symptoms, hospitalisations) • Steroid sparing • Rescue medication use (OCS/ICS) • HRQL (utilities) • Safety and tolerability • Adherence to treatment (via search strategy B)	Broadly consistent. All outcomes listed in final NICE scope are listed except the following which were queried by the ERG: • Patient and clinician evaluation of response: included in CS Appendix 8.6 • Mortality: included in CS p170-1 • Time to discontinuation: Not reported, though withdrawal rates reported in CS p62-65
Study design	• RCTs: for efficacy and/or safety data on mepolizumab and omalizumab (search strategy A) • Observational studies: for efficacy and/or safety data on omalizumab and mOCS (search strategy B)	Appropriate
Language	• Publications in all languages were included	Appropriate
Timeframe	• Conference proceedings from 2012 – 2014; assumed conference proceedings older than three years likely to have been published as full text articles (2015 abstracts not available at time of searching) • No time limit applied to all other publications and reports	Appropriate

CS = company submission; ERG = Evidence Review Group; HRQL = health-related quality of life; ICS = inhaled corticosteroids; mOCS = maintenance oral corticosteroids

4.1.3 Critique of data extraction

The technical report on the systematic review of clinical effectiveness[29] (a separate document to the CS) states that data were extracted by one reviewer and checked by a second reviewer.

4.1.4 Quality assessment

Quality assessment of RCTs and non-RCTs was undertaken using criteria adapted from the Centre for Reviews and Dissemination (CRD) guidance for undertaking systematic reviews.[30] The criteria for both appear appropriate. The reference to the CRD guidance for assessing non-RCTs is not provided in the CS but is provided in the technical report on the systematic review of clinical effectiveness.[29]

4.1.5 Evidence synthesis

For the two mepolizumab trials with a primary endpoint of reduction in exacerbations (DREAM and MENSA), meta-analyses were provided in the CS for some outcomes but not for others, and only for the ITT population (not for the two GSK proposed populations). Therefore, additional meta-analyses were requested by the ERG and provided in the clarification response (question A24). Meta-analysis was performed on individual patient data using a negative binomial regression model. Covariate modelling was applied separately to each study and to the combined dataset. Covariate adjustment for the meta-analysis included a covariate for study to allow for between-study differences.

Network meta-analyses (NMA) were undertaken to compare mepolizumab and omalizumab (discussed in Sections 4.3 and 4.4).

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Summary of excluded studies

Early studies not included in the clinical effectiveness section are reported in Table 3. Their exclusion from the main clinical and cost-effectiveness analysis appears appropriate.

1. **Moderate Asthma Study** (SB-240563/006, Flood-Page *et al*., 2007[31]) studied a moderate asthma population (not the licensed population) and did not show a benefit of mepolizumab (250mg and 750mg IV) for the primary endpoint peak expiratory flow. The study indicated the need for targeting a more severe population experiencing frequent exacerbations along with use of a biomarker of eosinophilic inflammation, such as sputum or peripheral blood eosinophils.

2. **Proof-of-concept Exacerbation Study** (CRT110184, Haldar *et al*., 2009[32]) was conducted in subjects with severe eosinophilic asthma and a history of recurrent severe exacerbations. It demonstrated a significant decrease in exacerbation frequency with 4-weekly administration of mepolizumab 750 mg IV compared with placebo over a 52-week treatment period and led to the Phase IIb /III clinical trial program. However, this study, which included patients selected on sputum eosinophil count, used an unlicensed dose and posology.

3. **Proof-of-concept OCS Reduction Study** (SB-240563/046, Nair *et al*., 2009[33]) was a 26-week, proof-of-concept study that assessed the ability of mepolizumab 750mg IV to allow prednisolone dose reduction in subjects with prednisolone-dependent asthma, without inducing an exacerbation. Subjects in the mepolizumab 750 mg IV group were able to reduce their mOCS dose to a greater extent than subjects on placebo whilst maintaining asthma control. However, this study, which included patients selected on sputum eosinophil count, used an unlicensed dose and posology.

Table 3: Summary of excluded mepolizumab studies (adapted from CS Table 9 and p40)

Trial no. (acronym)	Intervention	Comparator	Duration	Population	Primary endpoint	Primary study ref.
SB-240563/006 (Moderate Asthma Study)	IV mepolizumab 250mg and 750mg	IV placebo	12 weeks	Subjects with moderate, persistent asthma	Peak expiratory flow	Flood-Page, *et al*.[31]
CRT110184 (Proof of concept Exacerbation Study)	IV mepolizumab 750mg	IV placebo	52 weeks	Subjects with refractory eosinophilic asthma (based on sputum eosinophils) and a history of recurrent severe exacerbations	Clinically significant asthma exacerbations	Haldar, *et al*.[32]
SB-240563/046 (Proof of concept OCS Reduction Study)	IV mepolizumab 750mg	IV placebo	26 weeks	Subjects with prednisolone-dependent asthma and persistent sputum eosinophilia	Clinically significant asthma exacerbations Reduction in oral corticosteroid dose	Nair, *et al*.[33]

IV = intravenous; OCS = oral corticosteroids

4.2.2 Description of included studies

The evidence for mepolizumab within the CS is based mainly on data from three Phase IIb/III randomised controlled trials (RCTs) comparing add-on mepolizumab against placebo plus standard of care (SoC) in patients with severe asthma. Two trials (DREAM and MENSA) used a primary endpoint of reduction in exacerbations, whilst the third trial (SIRIUS) enrolled patients receiving oral corticosteroids and used a primary endpoint of reduction in corticosteroids. The inclusion of these three trials appears to be appropriate since they assessed the licensed dose and posology of mepolizumab (100mg SC) and/or a dose stated in the CS and summary EPAR[27] to be bioequivalent (75mg IV) and included patients with severe asthma, which was eosinophilic in nature in some or all patients.

In addition, two open-label extension studies (COSMOS and COLUMBA) enrolling patients from the three RCTs are discussed in Section 4.2.5.

4.2.2.1 Design of included RCTs

The three included mepolizumab RCTs are described below (also refer to Table 4 and Table 5).

1. **DREAM** (MEA112997, Pavord et al., 2012[19]) was a Phase IIb, double-blind, 52-week, dose-ranging RCT comparing mepolizumab (75mg, 250mg and 750mg IV) vs. placebo in patients with severe asthma which was likely to be eosinophilic. The ERG report only includes data from the 75mg IV group since this is stated in the CS and the mepolizumab summary EPAR[27] to be biologically equivalent to the licenced 100mg SC dose based on MENSA data (data for the 250mg and 750mg IV arms are omitted). The primary endpoint was clinically significant asthma exacerbations. Patients could enter the trial via any of four inclusion criteria: elevated blood eosinophils; elevated sputum eosinophils; elevated FeNO; or deterioration of asthma control following reduction in maintenance dose of either ICS or OCS. Modelling identified one inclusion criterion (blood eosinophil count) as a predictor of response to mepolizumab.

2. **MENSA** (MEA115588, Ortega *et al*., 2014[24]) was a Phase III, double-blind, 32-week RCT comparing mepolizumab (75mg IV and 100mg SC) vs. placebo. Subjects had severe eosinophilic asthma, defined as blood eosinophil count ≥300 cells/μL in the 12 months prior to screening or ≥150 cells/μL at screening. The primary endpoint was clinically significant asthma exacerbations.

3. **SIRIUS** (MEA115575, Bel *et al*., 2014[25]) was a Phase III, double-blind, 24-week RCT comparing mepolizumab (100mg SC) vs. placebo. Subjects had severe eosinophilic asthma, defined as blood eosinophil count ≥300 cells/μL in the 12 months prior to screening or ≥150 cells/μL at screening. All subjects were also receiving mOCS. There was a run-in phase prior to randomisation to ensure patients were receiving the lowest dose of corticosteroids that would maintain asthma control, and patients were eligible to be randomised if they had achieved a stable dose of OCS at the end of the run-in phase. The primary endpoint was reduction in OCS dose.

Table 4: Design of included trials (adapted from CS Table 9 and Table 12)

Trial	DREAM (MEA112997, Pavord *et al*. 2012[19])	MENSA (MEA115588, Ortega *et al*. 2014[24])	SIRIUS (MEA115575, Bel *et al*. 2014[25])
Trial design	Randomised, double-blind, placebo-controlled, parallel-group, dose-ranging	Randomised, double-blind, double-dummy, placebo-controlled, parallel-group	Randomised, double-blind, placebo-controlled, parallel-group
Duration	52 weeks	32 weeks	24 weeks
Interventions (n) and comparators (n)	Mepolizumab 75mg IV (n=153) every 4 weeks Mepolizumab 250mg IV (n=152) every 4 weeks Mepolizumab 750mg IV (n=156) every 4 weeks Placebo IV (n=155)	Mepolizumab 75mg IV (n=191) every 4 weeks Mepolizumab 100 SC (n=194) every 4 weeks Placebo SC & IV (n=191)	Mepolizumab 100mg SC (n=69) every 4 weeks Placebo SC (n=66)
Eligibility criteria	**Summary:** Severe asthma **General** • Severe eosinophilic asthma • Aged ≥12 years • Requirement for regular treatment with high dose ICS with or without maintenance OCS, in the previous 12 months. Also required to need additional maintenance treatment(s) (e.g., LABA, LTRA, or theophylline) • Pre-bronchodilator FEV_1 <80% predicted • History of ≥2 asthma exacerbations requiring treatment with systemic corticosteroids in the 12 months prior to Visit 1, despite use of high-dose ICS **Eosinophilia** Eosinophilic airway inflammation demonstrated at screening or in previous 12 months, by one of: • Elevated peripheral blood eosinophil level of ≥300 cells/µL *or* • Sputum eosinophils ≥3% *or* • Exhaled nitric oxide (FeNO) ≥50 ppb *or* • Prompt deterioration of asthma control (based on documented clinical history or objective measures) following ≤25% reduction in maintenance dose of inhaled or oral corticosteroid in previous 12 months	**Summary:** Severe eosinophilic asthma **General** • Same as DREAM **Eosinophilia** Eosinophilic airway inflammation characterised by one of the following: • Elevated peripheral blood eosinophil count of ≥300 cells/µL demonstrated in the past 12 months prior to screening *or* • Elevated peripheral blood eosinophil count of ≥150 cells/µL at screening	**Summary:** Severe eosinophilic asthma and receiving maintenance oral corticosteroids (mOCS) **General** • Severe eosinophilic asthma • Aged ≥12 years • Requirement for regular treatment with maintenance systemic corticosteroids (5.0 to 35 mg/day prednisolone or equivalent) and high-dose ICS (≥880 mcg/day [ex-actuator] FP or equivalent). At the end of the run-in period, patients eligible to be randomised if they had achieved a stable dose of OCS. • Pre-bronchodilator FEV_1 <80% predicted **Eosinophilia** Eosinophilic airway inflammation characterised by one of the following: • Elevated peripheral blood eosinophil count of ≥300 cells/µL demonstrated in the past12 months prior to screening *or* • Elevated peripheral blood eosinophil count of ≥150 cells/µL during the optimisation phase

Trial	DREAM (MEA112997, Pavord *et al*. 2012[19])	MENSA (MEA115588, Ortega *et al*. 2014[24])	SIRIUS (MEA115575, Bel *et al*. 2014[25])
Permitted concomitant medication	• Additional asthma medications such as theophyllines or LTRAs were permitted provided they had been taken regularly in the 3 months prior to randomisation (Visit 2, Week 0) • Maintenance OCS was permitted	• Same as DREAM	• Maintenance OCS required as per study eligibility criteria • Additional asthma medications such as theophylline or LTRA permitted provided they had been taken regularly in 3 months prior to randomisation (Visit 3)
Reference Trial identifier	Pavord ID, Howarth P, Bleecker ER *et al*. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012; 380(9842):651-9.[19] NCT01000506 https://clinicaltrials.gov/ct2/show/NCT01000506?term=Mepolizumab&rank=2	Ortega HG, Liu MC, Pavord ID *et al* Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma. N Engl J Med 2014; 371:1198-1207.[24] NCT01691521 https://clinicaltrials.gov/ct2/show/NCT01691521?term=Mepolizumab&rank=3	Bel EH, Wenzel SE, Thompson PJ *et al*. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. N Engl J Med 2014; 371:1189-1197.[25] NCT01691508 https://clinicaltrials.gov/ct2/show/NCT01691508?term=Mepolizumab&rank=9

FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; FP = fluticasone propionate; ICS = inhaled corticosteroids; IV = intravenous; LABA = long-acting beta agonist; LTRA = leukotriene receptor agonist; OCS = oral corticosteroids; SC = subcutaneous

Table 5: Outcomes and planned subgroup analyses in included trials (adapted from CS Table 12)

Trial	DREAM (MEA112997, Pavord *et al*. 2012[19])	MENSA (MEA115588, Ortega *et al*. 2014[24])	SIRIUS (MEA115575, Bel *et al*. 2014[25])
Primary outcomes	**Clinically significant asthma exacerbations** Frequency of clinically significant exacerbations of asthma as defined by worsening of asthma which required use of systemic corticosteroids and/or hospitalisation and/or emergency department (ED) visits. Use of systemic corticosteroids was defined as IV or oral steroid (e.g., prednisolone) for at least 3 days or a single IM dose.	**Clinically significant asthma exacerbations** Frequency of clinically significant exacerbations of asthma as defined by worsening of asthma which required use of systemic corticosteroids and/or hospitalisation and/or emergency department (ED) visits. Use of systemic corticosteroids was defined as IV or oral steroid (e.g., prednisolone) for at least 3 days or a single IM dose.	**Reduction of OCS** Percent reduction of OCS dose during Weeks 20-24 compared with the baseline dose, while maintaining asthma control, categorised as follows: • 90% to 100% • 75% to <90% • 50% to <75% • >0% to <50% • No decrease in OCS, lack of control during Weeks 20-24, or withdrawal from treatment.
Secondary/ other outcomes	**Secondary:** • Frequency of exacerbations requiring hospitalisation (including intubation and admittance to an intensive care unit) or ED visits • Mean change from baseline in clinic pre-	**Secondary:** • Frequency of exacerbations requiring hospitalisation (including intubation and admittance to an ICU) or ED visits • Frequency of exacerbations requiring hospitalisation	**Secondary:** • Proportion of subjects who achieved reduction of ≥50% in their daily OCS dose, compared with baseline dose • Proportion of subjects who achieved a reduction of OCS dose to ≤5.0 mg • Proportion of subjects who achieved a total reduction of

Trial	DREAM (MEA112997, Pavord *et al*. 2012[19])	MENSA (MEA115588, Ortega *et al*. 2014[24])	SIRIUS (MEA115575, Bel *et al*. 2014[25])
	bronchodilator FEV_1 at week 52 • Mean change from baseline in Asthma Control Questionnaire (ACQ) score at week 52 • Mean change in Asthma Quality of Life Questionnaire (AQLQ) score from baseline at week 52 **Other Efficacy Endpoints:** • Subject Rated Response to Therapy • Clinician Rated Response to Therapy • Mean change in EQ-5D health outcomes questionnaire score from baseline	• Mean change from baseline in clinic pre-bronchodilator FEV_1 at Week 32 • Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) at Week 32 **Other Efficacy Endpoints:** • Mean change from baseline in Asthma Control Questionnaire (ACQ-5) score at Week 32 • Subject Rated Response to Therapy • Clinician Rated Response to Therapy • Mean change from baseline in clinic post-bronchodilator FEV_1 at Week 32 • Work Productivity and Activity Impairment Index: General Health (WPAI:GH) • Resource utilisation measures	OCS dose • Median percentage reduction from baseline in daily OCS dose. **Other Efficacy Endpoints:** • Rate of clinically significant exacerbations • Rate of exacerbations requiring hospitalisation or ED visits • Rate of exacerbations requiring hospitalisation • Mean change from baseline in clinic pre-bronchodilator FEV_1 and in clinic post-bronchodilator FEV_1 at Week 24 • Mean change from baseline in ACQ-5 score at Week 24 • Mean change from baseline in SGRQ at Week 24 • Work Productivity and Activity Impairment Index: General Health (WPAI:GH) • Resource utilisation measures
Pre-planned subgroups (Further details found in the CRS for each study)	• Presence of each of the eosinophilic airways inflammation inclusion criteria • Age • Gender • Baseline percentage predicted pre-bronchodilator FEV_1 • Number of exacerbations in the year prior to the study • Region • Baseline use of maintenance oral corticosteroids (use vs. no use) • Baseline blood eosinophil count • Baseline total IgE concentration	• Age • Gender • Weight • Baseline Percent Predicted Pre-Bronchodilator FEV_1 • Number of Exacerbations in the year prior to the study • Region • Baseline Maintenance Oral Corticosteroid Therapy • Baseline Blood Eosinophil count • Baseline IgE Concentration • Prior Use of omalizumab (Xolair)	• Duration of Prior OCS Use • Baseline OCS Dose • Geographic Region • Baseline Blood Eosinophil count • Gender • Weight

ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; ED = emergency department; EQ-5D = EuroQol 5 Dimensions; ICU = intensive care unit; IM=intramuscular; IV = intravenous; OCS = oral corticosteroids; SGRQ = St. George's Respiratory Questionnaire; Work Productivity and Activity Impairment Index: General Health (WPAI:GH)

4.2.2.2 Quality assessment of included RCTs

The methodological quality of the three included mepolizumab RCTs was assessed (CS p73-74) using standard criteria adapted from the CRD guidance for undertaking systematic reviews.[34] Quality assessment results are provided in Table 6. All three studies were appropriately randomised and treatment allocation concealed. Blinding of care providers, participants and outcome assessors to treatment allocation was undertaken in all studies. The prognostic factors for the ITT populations were judged in the CS to be similar at baseline (see Section 4.2.2.7 for discussion of GSK populations). There were no unexpected imbalances in dropouts between groups in the ITT population. All studies included an analysis described in the CS as "ITT" but which the ERG would define as a well-recognised form of modified ITT (included all patients who were randomised and received at least one dose of study medication). However, the CS mainly focusses on the GSK populations rather than the ITT population.

Table 6: Quality assessment results for RCTs (reproduced from CS Table 19)

Trial number	DREAM	MENSA	SIRIUS
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination[34])			

4.2.2.3 Statistical analysis in included studies

For DREAM and MENSA, the rate of clinically significant exacerbations and rate of exacerbations requiring hospitalisation or ED visits were analysed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable) and baseline percent predicted pre-bronchodilator FEV_1, with the logarithm of time on treatment as an offset variable. This is an accepted approach for the analysis of exacerbation rates in COPD according to previous research.[35] Analysis of FEV_1, ACQ scores and AQLQ scores were performed using mixed model repeated measures methods (including covariates as above plus baseline value), visit and interaction terms for visit by baseline, and visit by treatment group. Analysis of SGRQ was performed using analysis of covariance with covariates as above plus baseline value.

In DREAM and MENSA, for the primary endpoint of exacerbations, for patients who withdrew, all data up to the time of patient withdrawal were included in the analyses. However, there are missing data for the period following withdrawal. The primary analysis made a standard assumption known as the Missing At Random (MAR) assumption. This assumes that future exacerbations for those who withdraw can be predicted from their exacerbation history prior to withdrawal and from the exacerbation rate of similar patients on the same treatment. Two sensitivity analyses were performed in which it was assumed that future exacerbations for patients who withdrew from a mepolizumab arm could be predicted based on the exacerbation rate in the placebo arm, not on the mepolizumab arm. Both analyses showed similar results to the primary analysis. The ERG is satisfied that the potential impact of missing data following withdrawal on the results of the analyses has been considered appropriately.

In SIRIUS, the primary efficacy endpoint was the percentage reduction in OCS dose during weeks 20-24 compared to the baseline dose, whilst maintaining asthma control. This was categorised as follows: 90% to 100% reduction; 75% to <90% reduction; 50% to <75% reduction; >0% to <50% reduction; or no reduction, lack of asthma control, or withdrawal from treatment. This was analysed using a proportional odds model for the above categories of oral steroid reduction, with covariates of region, number of years on oral steroids (<5 years versus ≥5 years), and baseline oral steroid dose. All subjects in the ITT population were included in the ITT analysis, whilst subjects who withdrew early or who had missing data were assigned to the lowest efficacy category. A sensitivity analysis assigning subjects to an efficacy category according to the dose reduction obtained by the time of withdrawal gave a similar result to the primary analysis. Analysis of the proportion of patients with specific reductions in oral steroid dose was performed using a binary logistic regression model with adjustment for covariates. The median percentage reduction in dose was analysed with the use of the Wilcoxon test. In SIRIUS, the rate of clinically significant exacerbations and rate of exacerbations requiring hospitalisation or ED visits were analysed using a negative binomial generalised linear model with a log-link function adjusting for covariates. Exacerbations requiring hospitalisation were not compared between treatment groups as there were no exacerbations requiring hospitalisation in the mepolizumab treatment arm.

The CS provides details of controlling for multiplicity across treatment comparisons and primary and secondary endpoints in DREAM and MENSA, presumably for the ITT analyses (CS p53-56). However, this is not mentioned in the CS for SIRIUS.

4.2.2.4 Statistical methods for subgroup analyses

In DREAM and MENSA, exploratory multivariate modelling was performed to investigate baseline variables predictive of the overall number of exacerbations and of differential efficacy of

mepolizumab (using covariates as above). The baseline covariates considered were: gender, age, weight, region, baseline % predicted FEV_1, airway reversibility, number of exacerbations in previous year, baseline blood eosinophil count, baseline use of maintenance OCS, and IgE level. Covariates for the main effects of the final model were chosen using backwards stepwise selection with a threshold of p=0.05 for the significance of each covariate. Interactions with treatment were then considered for all covariates.

The rate of clinically significant exacerbations was also analysed separately by subgroup (using covariates as above) and for possible airway inflammation characteristics. The CS states that no formal hypothesis testing in sub-groups of the populations was performed (CS p54-58); therefore it is not possible to make formal statements about statistically significant differences between subgroups. No multiplicity adjustment was made for conducting multiple subgroup analyses and the company therefore states that these results should be interpreted with caution (DREAM CSR p68).

In SIRIUS, further tabulations of the primary endpoint were performed to investigate the potential differential effects of mepolizumab; however, the CS states that these should be viewed with caution due to the small sample sizes within subgroups.

4.2.2.5 Participant flow in included studies (ITT populations)

The numbers of patients screened and randomised in the ITT populations of the three mepolizumab RCTs are shown in

Table **7**. The numbers of patients completing or withdrawing from RCTs and numbers continuing in an open-label extension study are shown in Table 8.

In DREAM, 888 patients were screened, 621 (70%) were randomised and 616 formed the ITT population (randomised and received study medications; this is actually a form of modified ITT [mITT] but this population is referred to in the ERG report as the ITT population for consistency with the CS). Of these, 520 (84%) completed the study, 96 (16%) withdrew and 28 (5%) withdrew due to adverse events (AEs). In MENSA, 802 patients were screened, 580 (72%) were randomised and 576 formed the ITT population. Of these, 539 (94%) completed the study, 37 (6%) withdrew and 5 (0.9%) withdrew due to AEs. In addition, 522 (91%) continued treatment in the open-label extension study, COSMOS. In SIRIUS, 185 patients were screened, 135 (73%) were randomised and all 135 formed the ITT population. In addition, 126 (93%) continued treatment in the open-label extension study, COSMOS. Of these, 128 (95%) completed the study, 7 (5%) withdrew and 6 (4%) withdrew due to AEs. The numbers withdrawing per group and the numbers withdrawing due to AEs were similar across groups in all studies.

Table 7: Patients screened and randomised in mepolizumab RCTs (adapted from CS p61-65)

	N (%)		
	DREAM	**MENSA**	**SIRIUS**
Screened	888	802	185
Not randomised (mainly due to not meeting inclusion or continuation criteria)	267 (30%)	222 (28%)	50 (27%)
Randomised	621 (70%)	580 (72%)	135 (73%)
ITT population (randomised and received study medication)	616 (69%)	576 (72%)	135 (73%)

ITT = intention-to-treat

Table 8: Patients in ITT populations completing or withdrawing from RCTs (adapted from CS p61-65)

	DREAM, N (%)					
ITT population[1]	**Placebo N=155**	**Mepo 75mg N=153**		**Mepo 250mg N=152**	**Mepo 750mg N=156**	**Total N=616**
Withdrawn	28 (18)	24 (16)		21 (14)	23 (15)	96 (16)
Withdrawn due to AE	6 (4)	5 (3)		8 (5)	9 (6)	28 (5)
Completed	127 (82)	129 (84)		131 (86)	133 (85)	520 (84)
Entered open-label extension study (COLUMBA)						347 (56%)
	MENSA, N (%)					
ITT population[1]	**Placebo N=191**	**Mepo 75mg IV N=191**	**Mepo 100mg SC N=194**			**Total N=576**
Withdrawn	12 (6)	16 (8)	9 (5)			37 (6)
Withdrawn due to AE	4 (2)	0	1 (0.5)			5 (0.9)
Completed	179 (94)	175 (92)	185 (95)			539 (94)
Entered open-label extension study (COSMOS)	175 (90)	171 (90)	176 (91)			522 (91)
	SIRIUS, N (%)					
ITT population[1]	**Placebo N=66**		**Mepo 100mg SC N=69**			**Total N=135**
Withdrawn	4 (6)		3 (4)			7 (5)
Withdrawn due to AE	3 (5)		3 (4)			6 (4)
Completed	62 (94)		66 (96)			128 (95)
Entered open-label extension study (COSMOS)	61 (92)		65 (94)			126 (93)

[1]ITT (intention-to-treat) population: randomised and received at least one dose of study medication; IV = intravenous; SC = subcutaneous

4.2.2.6 Numbers of patients in ITT and GSK populations per trial

Table 9 shows the numbers of patients within each of the four sub-populations defined above, for the three pivotal trials of mepolizumab.

Table 9: Numbers of patients randomised and in each population per trial

	DREAM			MENSA				SIRIUS		
	Placebo	Mepo 75mg IV	Total[1]	Placebo	Mepo 100mg SC	Mepo 75mg IV	Total	Placebo	Mepo 100mg SC	Total
ITT population	155	153	308	191	194	191	576	66	69	135
GSK PP	56	54	110	64	78	65	207	48	54	102
GSK PP excl. stable mOCS	32	39	71	45	54	48	147	15	22	37
Stable mOCS	24	15	39	19	24	17	60	33	32	65

[1]Total relevant to this appraisal i.e. placebo or mepolizumab 100mg SC or 75mg IV. GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; IV = intravenous; mOCS = maintenance oral corticosteroids; SC = subcutaneous

4.2.2.7 Baseline characteristics of patients in included RCTs

ITT population: The demographics and baseline characteristics of patients recruited for DREAM, MENSA and SIRIUS (Table 10) were generally similar across most key variables, such as age (mean approximately 50 years), gender (approximately 60% female), BMI (mean approximately 28 kg/m$^{2)}$, duration of asthma (mean approximately 20 years) and mean blood eosinophil count (240-290 cells/μL). The mean number of exacerbations in the previous year was approximately 3.6 in all three studies; however, all patients in MENSA and DREAM had ≥2 exacerbations in the previous year compared to 67% in SIRIUS. The percentage of patients on baseline mOCS was 31% in DREAM, 25% in MENSA and 100% in SIRIUS.

The CS reports that there were no notable differences between the treatment groups within each study for the ITT populations for the DREAM and MENSA trials (CS, p66), however data were provided only for the trial as a whole, rather than by study arm (Table 10). There were some differences between treatment groups in the SIRIUS trial, but these did not consistently favour one arm.

Table 10: Demographic characteristics for ITT populations (CS p66 and Appendix 8.3 and CSRs)

	DREAM (N=616)		MENSA (N=576)		SIRIUS (N=135)		
Demographic	**Placebo N=155**	**Mepolizumab All doses N=461**	**Placebo N=191**	**Mepolizumab Both doses N=385**	**Placebo N=66**	**Mepolizumab 100 mg SC N=69**	**Overall N=135**
Age, yr							
Mean (SD)	48.6 (11.28)		50.1 (14.28)		49.9 (10.30)	49.8 (14.10)	49.9 (12.34)
Min, max	15, 74		12, 82		28, 70	16, 74	16, 74
Gender, (%)							
Female	63%		57%		45%	64%	55%
Race, (%)							
White	90%		78%		92%	97%	95%
Body Mass Index, kg/m^2							
Mean (SD)	28.5 (5.95)		27.77 (5.830)		29.52 (6.047)	27.84 (5.895)	28.66 (6.007)
Duration of Asthma, yr							NR
Mean (SD)	19.1 (14.3)		19.9 (13.8)		20.1 (14.37)	17.4 (11.79)	
Blood Eosinophils (cell/µL)							
Geometric mean	250		290		230	250	NR
Exacerbations in previous year							
Mean (SD)	3.6 (3.1)		3.6 (2.6)		2.9 (2.76)	3.3 (3.39)	3.1 (3.10)
≥2 (%)	614 (99.7%)		575 (99.8%)		45 (68%)	46 (67%)	91 (67%)
≥4 (%)	NR		189 (33%)		20 (30%)	28 (41%)	48 (36%)
≥1 Exacerbation requiring hospitalisation in previous year (%)	150 (24%)		109 (19%)		9 (14%)	14 (20%)	23 (17%)
On mOCS (%)	188 (31)		144 (25%)		66 (100%)	69 (100%)	135 (100%)
Screening Daily OCS Dose							
Mean (SD), mg	17.4 (16.77)		13.2 (11.89)		15.2 (6.71)	15.1 (9.31)	NR

CSR = clinical study report; ED = emergency department; mOCS = maintenance oral corticosteroids; NR = not reported; SC = subcutaneous; SD = standard deviation; yr = years

Baseline characteristics: "GSK PP" and "GSK PP excl. stable mOCS" populations

The baseline characteristics of patients in the two GSK populations (GSK PP and GSK PP excl. stable mOCS) are presented in Table 11 (DREAM), Table 12 (MENSA) and Table 13 (SIRIUS). These data are generally comparable with the ITT population (Table 10), but with some noticeable differences due to the selection criteria for the GSK populations.

First, the baseline rate of exacerbations in the previous 12 months is much higher in the two GSK populations (GSK PP and GSK PP excl. stable mOCS) in DREAM (5.2 and 6.7 respectively) and MENSA (5.1 and 6.2 respectively) than in the corresponding ITT populations (3.6 for DREAM and 3.6 for MENSA). Conversely, for SIRIUS the baseline exacerbation rate was similar for the ITT population (3.1) and GSK PP (3.2). In MENSA, the percentage of patients with ≥4 exacerbations in the previous year was 100% in the GSK PP excl. stable mOCS and 71% in the GSK PP versus 33% in the ITT population. Conversely, in SIRIUS the percentage with ≥4 exacerbations was the same (36%) in the GSK PP and ITT populations. These data were not reported for DREAM.

There was a considerable difference in the baseline blood eosinophil count between the GSK and ITT populations. In DREAM, the two GSK populations had mean counts per group of 380 to 510 cells/μL, whereas the ITT population had a mean of 250 cells/μL Table 10. In MENSA, the two GSK populations had mean counts per group of 440 to 510 cells/μL, whereas the ITT population had a mean of 290 cells/μL. In SIRIUS, the mean count per group was 370 to 420 cells/μL in the GSK PP, versus 230 to 250 cells/μL in the ITT population.

In DREAM, the percentage of patients on baseline mOCS was 66% in the GSK PP and 46% in the GSK PP excl. stable mOCS, compared with 31% in the ITT population. In MENSA, the percentage of patients on baseline mOCS was 48% in the GSK PP and 28% in the GSK PP excl. stable mOCS, compared with 25% in the ITT population. In SIRIUS, all patients were on baseline mOCS Table 10.

The baseline characteristics were generally consistent between treatment arms within the individual trials. In MENSA, the proportion of patients requiring ≥1 hospitalisation in the previous year was slightly higher in the placebo group than the mepolizumab groups, whilst in SIRIUS this was slightly higher for mepolizumab than placebo (little overall difference in DREAM). The mean baseline OCS daily dose was higher in the placebo arm in MENSA but higher in the mepolizumab arms in DREAM (little difference in SIRIUS). In SIRIUS, the percentage of female subjects was higher in the mepolizumab group (69% vs. 48% in the GSK PP), as was the SGRQ score (50.1 vs. 43.6 in the GSK PP).

Table 11: DREAM demographic characteristics for GSK PPs (adapted from clarification response A23)

	GSK PP excl. stable mOCS					GSK PP				
	Placebo	**Mepo 75mg IV**	**Mepo 250mg IV**	**Mepo 750mg IV**	**Total**	**Placebo**	**Mepo 75mg IV**	**Mepo 250mg IV**	**Mepo 750mg IV**	**Total**
Demographic	**n=32**	**n=39**	**n=29**	**n=34**	**n=134**	**n=56**	**n=54**	**n=51**	**n=51**	**n=212**
Age, years Mean (SD) Min, max	47.3 (11.86) 23, 67	50.9 (10.71) 24, 69	49.9 (10.61) 22, 66	46.0 (12.53) 19, 64	48.6 (11.50) 19, 69	49.4 (10.92) 23, 67	50.7 (10.58) 24, 69	50.2 (11.66) 22, 73	48.2 (11.87) 19, 66	49.6 (11.22) 19, 73
Gender, (%) Female	22 (69%)	28 (72%)	18 (62%)	26 (76%)	94 (70%)	34 (61%)	39 (72%)	26 (51%)	36 (71%)	135 (64%)
Race, (%) Not Hispanic or Latino	29 (91%)	38 (97%)	28 (97%)	30 (88%)	125 (93%)	51 (91%)	50 (93%)	50 (98%)	45 (88%)	196 (92%)
Weight, kg, Mean (SD)	80.1 (17.97)	74.8 (15.46)	81.4 (18.03)	77.8(18.96)	78.2 (17.54)	79.9 (17.03)	75.3 (15.56)	82.7 (17.56)	81.2 (18.43)	79.7 (17.25)
Duration of asthma, years										
≥1 to <5 years	3(9%)	4(10%)	2(7%)	4(12%)	13(10%)	8(14%)	6(11%)	4(8%)	6(12%)	24(11%)
≥5 to <10 years	4(13%)	8(21%)	5(17%)	6(18%)	23(17%)	11(20%)	10(19%)	9(18%)	8(16%)	38(18%)
≥10 to <15 years	8(25%)	7(18%)	5(17%)	1(3%)	21(16%)	12(21%)	8(15%)	8(16%)	4(8%)	32(15%)
≥15 to <20 years	1(3%)	2(5%)	3(10%)	6(18%)	12(9%)	1(2%)	5(9%)	3(6%)	7(14%)	16(8%)
≥20 to <25 years	7(22%)	6(15%)	2(7%)	6(18%)	21(16%)	8(14%)	7(13%)	8(16%)	8(16%)	31(15%)
≥25 years	9(28%)	12(31%)	12(41%)	11(32%)	44(33%)	16(29%)	18(33%)	19(37%)	18(35%)	71(33%)
Blood Eosinophils (cell/µL) Geometric mean	450	400	510	480		450	380	440	430	
Exacerbations in previous year Mean (SD) ≥2 (%) ≥4 (%)	8.0 (6.55) 32 (100%) NR	6.7 (4.66) 39 (100%) NR	6.0 (3.07) 29 (100%) NR	6.0 (3.60) 34 (100%) NR	6.7 (4.70) 134 (100%) NR	5.7 (5.60) 56 (100%) NR	5.6 (4.40) 54 (100%) NR	4.5 (2.89) 51 (100%) NR	4.8 (3.37) 51 (100%) NR	5.2 (4.24) 212 (100%) NR
≥1 Exacerbation requiring hospitalisation in previous year (%)	8 (25%)	8 (21%)	9 (31%)	6 (18%)	31 (23%)	13 (23%)	9 (17%)	12 (24%)	10 (20%)	44 (21%)
On mOCS (%)	13 (41%)	20 (51%)	11 (38%)	18 (53%)	62 (46%)	37 (66%)	35 (65%)	33 (65%)	35 (69%)	140 (66%)
Baseline OCS daily dose (prednisolone equivalent) Mean (SD), mg	14.5 (14.39)	21.2 (17.18)	37.0 (45.51)	18.1 (16.99)	21.7 (24.70)	15.6 (12.66)	19.2 (14.72)	20.7 (28.98)	15.6 (13.29)	17.7 (18.33)
Baseline ACQ-5 Mean Score	2.7 (1.20)	2.4 (1.29)	2.5 (1.33)	2.8 (1.35)	2.6 (1.29)	2.6 (1.19)	2.4 (1.18)	2.7 (1.33)	2.5 (1.34)	2.5 (1.25)
Baseline EQ5D Total Score Mean (SD)	**n=24** 0.78 (0.209)	**n=15** 0.77 (0.145)	**n=22** 0.73 (0.254)	**n=17** 0.68 (0.319)		**n=56** 0.80 (0.180)	**n=54** 0.73 (0.226)	**n=51** 0.74 (0.191)	**n=51** 0.71 (0.280)	

ACQ = Asthma Control Questionnaire; GSK PP = GlaxoSmithKline proposed population; IV = intravenous; mOCS = maintenance oral corticosteroids; NR = not reported; SD = standard deviation

Table 12: MENSA demographic characteristics for GSK PPs (adapted from CS Table 17)

	GSK PP excl. stable mOCS				GSK PP			
	Placebo	**Mepo 75mg IV**	**Mepo 100mg SC**	**Total**	**Placebo**	**Mepo 75mg IV**	**Mepo 100mg SC**	**Total**
Demographic	**n=45**	**n=48**	**n=54**	**n=147**	**n=64**	**n=65**	**n=78**	**n=207**
Age, years								
Mean (SD)	47.3 (14.88)	51.8 (14.05)	53.7 (12.59)	51.1 (13.96)	48 (14.19)	50.8 (14.64)	53.1 (12.31)	50.8 (13.76)
Min, max	12, 69	17, 82	16, 77	12, 82	12, 73	15, 82	16, 77	12, 82
Gender, (%) Female	23 (51%)	27 (56%)	34 (63%)	84 (57%)	33 (52%)	37 (57%)	47 (60%)	117 (57%)
Race, (%) Not Hispanic or Latino	44 (98%)	44 (92%)	51 (94%)	139 (95%)	62 (97%)	59 (91%)	75 (96%)	196 (95%)
Weight, kg, Mean (SD)	76.2 (19.36)	77.09 (16.418)	77.43 (23.482)	76.94 (20.004)	77.76 (20.718)	75.6 (16.851)	75.78 (21.027)	76.33 (19.638)
Duration of asthma, years								
Mean (SD)	18.7 (15.02)	17.6 (14.05)	19.6 (11.97)	18.7 (13.57)	19.9 (15.38)	17.8 (14.43)	20.7 (13.05)	19.6 (14.22)
≥1 to <5 years	8 (18%)	8 (17%)	2 (4%)	18 (12%)	9 (14%)	12 (18%)	5 (6%)	26 (13%)
≥5 to <10 years	7 (16%)	10 (21%)	9 (17%)	26 (18%)	10 (16%)	11 (17%)	13 (17%)	34 (16%)
≥10 to <15 years	7 (16%)	7 (15%)	15 (28%)	29 (20%)	10 (16%)	11 (17%)	17 (22%)	38 (18%)
≥15 to <20 years	6 (13%)	5 (10%)	4 (7%)	15 (10%)	9 (14%)	7 (11%)	5 (6%)	21 (10%)
≥20 to <25 years	3 (7%)	6 (13%)	8 (15%)	17 (12%)	4 (6%)	6 (9%)	11 (14%)	21 (10%)
≥25 years	14 (31%)	12 (25%)	16 (30%)	42 (29%)	22 (34%)	18 (28%)	27 (35%)	67 (32%)
Blood Eosinophils (cell/µL) Geometric mean	480	440	510		460	460	480	
Exacerbations in previous year								
Mean (SD)	6.5 (3.74)	5.9 (2.49)	6.1 (3.29)	6.2 (3.19)	5.3 (3.67)	5 (2.61)	5 (3.25)	5.1 (3.19)
≥2 (%)	45 (100%)	48 (100%)	54 (100%)	147 (100%)	64 (100%)	65 (100%)	78 (100%)	207 (100%)
≥4 (%)	45 (100%)	48 (100%)	54 (100%)	147 (100%)	45 (70%)	48 (74%)	54 (69%)	147 (71%)
≥1 Exacerbation requiring hospitalisation in previous year (%)	18 (40%)	16 (33%)	15 (28%)	49 (33%)	21 (33%)	23 (35%)	18 (23%)	62 (30%)
On mOCS (%)	14 (31%)	14 (29%)	13 (24%)	41 (28%)	33 (52%)	29 (45%)	37 (47%)	99 (48%)
Baseline OCS daily dose (prednisolone equivalent) Mean (SD), mg	17.5 (19.69)	13.6 (11.88)	14.3 (12.61)	15.1 (14.92)	14.6 (15.73)	11.3 (9.89)	11.9 (10.82)	12.6 (12.4)
Baseline ACQ-5,	**n=45**	**n=48**	**n=53**		**n=64**	**n=65**	**n=76**	
Mean Score	2.49 (1.425)	2.25 (1.071)	2.36 (1.13)		2.39 (1.323)	2.28 (1.088)	2.46 (1.181)	
Baseline SGRQ	**n=45**	**n=48**	**n=54**		**n=64**	**n=65**	**n=77**	
Total Score, Mean (SD)	52.2 (20.67)	47.5 (18.48)	51.8 (19.11)		50.2 (19.91)	48.7 (18.9)	50.9 (19.49)	

ACQ = Asthma Control Questionnaire; GSK PP = GlaxoSmithKline proposed population; IV = intravenous; mOCS = maintenance oral corticosteroids; SC = subcutaneous; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire

Table 13: SIRIUS Demographic Characteristics for GSK PP (adapted from CS Table 18)

	GSK PP		
	Placebo	**Mepo 100mg SC**	**Total**
Demographic	**n=48**	**n=54**	**n=102**
Age, yr Mean (SD) Min, max	 49.2 (9.92) 28, 69	 50 (14.53) 16, 74	 49.6 (12.52) 16, 74
Gender, (%) Female	23 (48%)	37 (69%)	60 (59%)
Race, (%) Not Hispanic or Latino	45 (94%)	52 (96%)	97 (95%)
Weight, kg, Mean (SD)	86.06 (20.158)	77.57 (16.926)	81.56 (18.909)
Duration of asthma, years Mean (SD)	19.6 (13.92)	17.4 (11.44)	18.4 (12.65)
≥1 to <5 years	7 (15%)	5 (9%)	12 (12%)
≥5 to <10 years	7 (15%)	12 (22%)	19 (19%)
≥10 to <15 years	6 (13%)	5 (9%)	11 (11%)
≥15 to <20 years	8 (17%)	9 (17%)	17 (17%)
≥20 to <25 years	4 (8%)	8 (15%)	12 (12%)
≥25 years	16 (33%)	15 (28%)	31 (30%)
Blood Eosinophils (cell/µL) Geometric mean	370	420	
Exacerbations in previous year Mean (SD) ≥2 (%) ≥4 (%)	 3.0 (2.78) 32 (67%) 15 (31%)	 3.3 (3.54) 33 (61%) 22 (41%)	 3.2 (3.19) 65 (64%) 37 (36%)
≥1 Exacerbation requiring hospitalisation in previous yr (%)	7 (15%)	11 (20%)	18 (18%)
On mOCS (%)	48 (100%)	54 (100%)	102 (100%)
Baseline OCS daily dose (prednisolone equivalent) Mean (SD), mg	11.7 (4.93)	12.1 (7.3)	11.9 (6.27)
Duration of OCS use ≥5 years (%)	22 (46%)	28 (52%)	50 (49%)
Baseline ACQ-5 Mean Score	2.06 (1.172)	2.16 (1.162)	
Baseline SGRQ Total Score Mean (SD)	43.6 (17.38)	50.1 (16.3)	

ACQ = Asthma Control Questionnaire; GSK PP = GlaxoSmithKline proposed population; OCS = oral corticosteroids; SC = subcutaneous; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire

4.2.3 Clinical effectiveness results for mepolizumab

4.2.3.1 Clinical effectiveness in ITT and GSK populations

The CS provides effectiveness data for the three included trials, two focussing on exacerbation reduction (MENSA and DREAM) and one focussing on OCS dose reduction (SIRIUS). There are some inconsistencies between different sections of the CS in terms of whether the data presented are based on a single trial or a meta-analysis, and also whether the presented mepolizumab data are based on the 100mg SC arms only (as per licence) or the combined 100mg SC and 75mg IV arms (these are stated in the CS and in the summary EPAR for mepolizumab[27] to be bioequivalent). Additional data

were requested from the company during clarification and are included in the results presented in this section.

The ERG has tabulated the clinical effectiveness data showing the ITT population and the three additional populations for all three trials (and meta-analyses of these) side-by-side (Table 14 to Table 23). Some of these data are presented in various different sections of the CS, whilst some were provided by the company on request by the ERG. The subgroup analyses are described in Section 4.2.4.2, including those used as the basis for the GSK proposed populations.

Clinically significant exacerbations

Table 14 shows the rates of clinically significant exacerbations in all three trials (and meta-analysed across trials) in the ITT population, the two GSK populations and the stable mOCS population. Clinically significant exacerbations are defined as worsening of asthma requiring use of systemic corticosteroids and/or hospitalisation and/or emergency department (ED) visits. Use of systemic corticosteroids was defined as IV or oral steroid (e.g. prednisolone) for at least 3 days or a single intramuscular dose. For subjects on maintenance systemic corticosteroids, at least double the existing dose for at least 3 days was required to be categorised as a clinically significant exacerbation.

Clinical advisors to the ERG advised that exacerbations requiring either systemic corticosteroids or hospitalisation were more robust indicators of a severe exacerbation than ED visits, because some patients may visit the ED for minor reasons such as loss of an inhaler. However, clinically significant exacerbations as defined in the CS included ED visits.

The rate ratios (RRs) for clinically significant exacerbations for mepolizumab (100mg SC and 75mg IV groups combined) vs. placebo, meta-analysed across MENSA and DREAM, were as follows (Table 14): RR=0.51 (95% CI 0.42, 0.62) in the ITT population; RR=0.41, 95% CI 0.31, 0.55) in the GSK PP; RR=0.35 (95% CI 0.25, 0.50) in the GSK PP excl. stable mOCS; and RR=0.55 (95% CI 0.32, 0.92) in the stable mOCS population. Therefore, as expected, results were more favourable for the GSK PP than the ITT population, and even more favourable for the GSK PP excl. stable mOCS, but less favourable for the stable mOCS group. In SIRIUS, the OCS-sparing study, RRs for exacerbations were slightly less favourable than in MENSA and DREAM: RR=0.68 (95% CI 0.47, 0.99) in the ITT population; RR=0.77 (95% CI 0.51, 1.17) in the GSK PP; RR=0.81 (95% CI 0.40, 1.64) in the GSK PP excl. stable mOCS; and RR=0.75 (95% CI 0.44, 1.29) in the stable mOCS population.

Table 14: Results for clinically significant exacerbations

	ITT				GSK PP				GSK PP excl. stable mOCS				Stable mOCS			
	Placebo	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**
	MENSA															
N	191	194	191	385	64	78	65		45	54	48		19	24	17	
Rate/year	1.75	0.81	0.93	0.877 (model)	2.65	1.32	1.06	1.206 (model)	3.10	1.22	1.20	1.213 (model)	1.4	1.3	0.63	
Rate ratio (mepo/pbo)		**0.47**	**0.53**	**0.50**		**0.50**	**0.40**	Not provided		**0.39**	**0.39**	Not provided		**0.93**	**0.45**	Not provided
95% CI		0.35, 0.63	0.39, 0.71	0.39, 0.64		0.32, 0.78	0.24, 0.67			0.23, 0.67	0.22, 0.68			0.42, 2.03	0.16, 1.24	
p-value		<0.001	<0.001	<0.001		0.002	<0.001			<0.001	<0.001			0.855	0.121	
	DREAM															
N	155		153	153	56		54	54	32		39	39	24		15	15
Rate/year	2.40		1.24	1.24	3.08		1.12	1.12	3.64		1.13	1.13	2.8		1.15	1.15
Rate ratio (mepo/pbo)			**0.52**	**0.52**			**0.36**	**0.36**			**0.31**	**0.31**			**0.41**	**0.41**
95% CI			0.39, 0.69	0.39, 0.69			0.24, 0.55	0.24, 0.55			0.18, 0.53	0.18, 0.53			0.19, 0.86	0.19, 0.86
p-value			<0.001	<0.001			<0.001	<0.001			<0.001	<0.001			0.019	0.019
	SIRIUS															
N	66	69		69	48	54		54	15	22		22	33	32		32
Rate/year	2.12	1.44		1.44	2.1	1.62		1.62	2.16	1.75		1.75	2.05	1.54		1.54
Rate ratio (mepo/pbo)		**0.68**		**0.68**		**0.77**		**0.77**		**0.81**		**0.81**		**0.75**		**0.75**
95% CI		0.47, 0.99		0.47, 0.99		0.51, 1.17		0.51, 1.17		0.40, 1.64		0.40, 1.64		0.44, 1.29		0.44, 1.29
p-value		0.042		0.042		0.222		0.222		0.556		0.556		0.298		0.298
	DREAM & MENSA meta-analysis															
N	346			538	120			197	77			141	43			56
Rate ratio (mepo/pbo)			Not requested	**0.51**			Not requested	**0.41**			Not requested	**0.35**			Not requested	**0.55**
95% CI				0.42, 0.62				0.31, 0.55				0.25, 0.50				0.32, 0.92
p-value				<0.001				<0.001				<0.001				0.023
	DREAM & MENSA & SIRIUS meta-analysis															
N					168			251	92			163	76			88
Rate ratio (mepo/pbo)			Not possible – different covariates				Not requested	**0.50**			Not requested	**0.42**			Not requested	**0.64**
95% CI								0.40, 0.64				0.30, 0.57				0.44, 0.93
p-value								<0.001				<0.001				0.019

Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. CI = confidence interval; GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; IV = intravenous; mOCS = maintenance oral corticosteroids; SC = subcutaneous

Exacerbations requiring hospitalisation

Table 15 shows the rates of exacerbations requiring hospitalisation in all three trials (and meta-analyses) in the different sub-populations. The RRs for mepolizumab (100mg SC and 75mg IV groups combined) vs. placebo, meta-analysed across MENSA and DREAM, were as follows: RR=0.50 (95% CI 0.28, 0.89) in the ITT population; RR=0.44 (95% CI 0.19, 1.02) in the GSK PP; RR=0.43 (95% CI 0.16, 1.12) in the GSK PP excl. stable mOCS; and RR=0.53 (95% CI 0.10, 2.75) in the stable mOCS population. In SIRIUS the numbers were low (ITT population: 7 hospitalisations in the placebo group vs. 0 in the mepolizumab group) so RRs could not be calculated.

Exacerbations requiring hospitalisation or emergency department visits

Table 16 shows the rates of exacerbations requiring hospitalisation or ED visits. The RRs for mepolizumab (100mg SC and 75mg IV groups combined) vs. placebo, meta-analysed across MENSA and DREAM, were as follows: RR=0.53 (95% CI 0.33, 0.84) in the ITT population; RR=0.38, 95% CI 0.19, 0.74) in the GSK PP; RR=0.32 (95% CI 0.14, 0.73) in the GSK PP excl. stable mOCS; and RR=0.54 (95% CI 0.17, 1.68) in the stable mOCS population Data for SIRIUS were relatively similar (Table 16).

Table 15: Results for exacerbations requiring hospitalisation

	ITT				GSK PP				GSK PP excl. stable mOCS				Stable mOCS			
	Placebo	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**
	MENSA															
N	191	194	191	385	64	78	65		45	54	48		19	24	17	
Rate/year	0.10	0.03	0.06	0.05	0.29	0.16	0.08		0.35	0.17	0.07		0.07	0.07	0.07	
Rate ratio (mepo/pbo)		**0.31**	**0.61**	**0.44**		**0.55**	**0.28**	Not provided		**0.49**	**0.19**	Not provided		**0.96**	**0.98**	Not provided
95% CI		0.11, 0.91	0.23, 1.66	0.19, 1.02		0.15, 2.03	0.05, 1.45			0.11, 2.11	0.03, 1.31			0.06, 16.84	0.06, 16.60	
p-value		0.034	0.334	0.056		0.372	0.129			0.338	0.091			0.979	0.986	
	DREAM															
N	155		153	153	56		54	54	32		39	39	24		15	15
Rate/year	0.18		0.11	0.11	0.39		0.17	0.17	0.32		0.16	0.16	0.65		0.21	0.21
Rate ratio (mepo/pbo)			**0.61**	**0.61**			**0.45**	**0.45**			**0.50**	**0.50**			**0.33**	**0.33**
95% CI			0.28, 1.33	0.28, 1.33			0.14, 1.43	0.14, 1.43			0.13, 1.97	0.13, 1.97			0.04, 2.99	0.04, 2.99
p-value			0.214	0.214			0.173	0.173			0.322	0.322			0.321	0.321
	SIRIUS															
N	66	69		69	48	54		54	15	22		22	33	32		32
Rate/year	7 events	0 events		0 events	Insufficient events				Insufficient events				Insufficient events			
Rate ratio (mepo/pbo)																
95% CI																
p-value																
	DREAM & MENSA meta-analysis															
N	346			538	120			197	77			141	43			56
Rate ratio (mepo/pbo)			Not requested	**0.50**			Not requested	**0.44**			Not requested	**0.43**			Not requested	**0.53**
95% CI				0.28, 0.89				0.19, 1.02				0.16, 1.12				0.10, 2.75
p-value				0.018				0.057				0.085				0.452
	DREAM & MENSA & SIRIUS meta-analysis															
N							Insufficient events				Insufficient events				Insufficient events	
Rate ratio (mepo/pbo)			Not possible – different covariates													
95% CI																
p-value																

Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, region, and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. CI = confidence interval; GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; IV = intravenous; mOCS = maintenance oral corticosteroids; SC = subcutaneous

Table 16: Results for exacerbations requiring hospitalisation or emergency department visits

	ITT				GSK PP				GSK PP excl. stable mOCS				Stable mOCS			
	Placebo	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**
	MENSA															
N	191	194	191	385	64	78	65		45	54	48		19	24	17	
Rate/year	0.20	0.08	0.14	0.11	0.52	0.26	0.16		0.59	0.26	0.12		0.23	0.06	0.25	
Rate ratio (mepo/pbo)		**0.39**	**0.68**	**0.52**		**0.49**	**0.31**	Not provided		**0.45**	**0.21**	Not provided		**0.25**	**1.1**	Not provided
95% CI		0.18, 0.83	0.33, 1.41	0.28, 0.96		0.19, 1.31	0.10, 0.99			0.14, 1.44	0.05, 0.88			0.03, 2.49	0.21, 5.86	
p-value		0.015	0.299	0.037		0.157	0.048			0.177	0.033			0.239	0.909	
	DREAM															
N	155		153	153	56		54	54	32		39	39	24		15	15
Rate/year	0.43		0.17	0.17	0.63		0.21	0.21	0.56		0.16	0.16	0.7		0.33	0.33
Rate ratio (mepo/pbo)			**0.40**	**0.40**			**0.33**	**0.33**			**0.29**	**0.29**			**0.47**	**0.47**
95% CI			0.19, 0.81	0.19, 0.81			0.12, 0.92	0.12, 0.92			0.08, 1.06	0.08, 1.06			0.09, 2.62	0.09, 2.62
p-value			0.011	0.011			0.034	0.034			0.060	0.060			0.391	0.391
	SIRIUS															
N	66	69		69	48	54		54	15	22		22	33	32		32
Rate/year	0.22	0.08		0.08	0.2	0.07		0.07	Insufficient events				0.17	0.1		0.1
Rate ratio (mepo/pbo)		**0.35**		**0.35**		**0.33**		**0.33**						**0.59**		**0.59**
95% CI		0.09, 1.40		0.09, 1.40		0.06, 1.72		0.06, 1.72						0.09, 3.71		0.09, 3.71
p-value		0.136		0.136		0.189		0.189						0.572		0.572
	DREAM & MENSA meta-analysis															
N	346			538	120			197	77			141	43			56
Rate ratio (mepo/pbo)			Not requested	**0.53**			Not requested	**0.38**			Not requested	**0.32**			Not requested	**0.54**
95% CI				0.33, 0.84				0.19, 0.74				0.14, 0.73				0.17, 1.68
p-value				0.007				0.004				0.007				0.284
	DREAM & MENSA & SIRIUS meta-analysis															
N					168			251			Insufficient events		76			88
Rate ratio (mepo/pbo)			Not possible – different covariates				Not requested	**0.37**							Not requested	**0.55**
95% CI								0.20, 0.69								0.21, 1.45
p-value								0.002								0.227

Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. Note: Canada combined with Rest of World within the covariate of region. CI = confidence interval; GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; IV = intravenous; mOCS = maintenance oral corticosteroids; SC = subcutaneous

Pre-bronchodilator FEV_1

Table 17 shows the differences in scores for pre-bronchodilator FEV_1. The differences in FEV_1 for mepolizumab (100mg SC group) vs. placebo in MENSA were as follows: 98 ml (95% CI 11, 184) in the ITT population; 116 ml (95% CI -41, 272) in the GSK PP; and 107 ml (95% CI -95, 309) in the GSK PP excl. stable mOCS; no data were provided for the stable mOCS population. The CS states that these results reach clinical though not statistical significance (CS p88). Data from MENSA for the mepolizumab 75mg IV group were similar (Table 17).

In DREAM, the difference in FEV_1 for mepolizumab vs. placebo in the ITT population was much smaller (3 ml) than in MENSA (98ml and 100 ml; Table 17); the reason for this is not clear. Data for other DREAM populations, or for other sub-populations and meta-analyses, were not reported in the CS or requested by the ERG (Table 17).

Quality of life: St. George's Respiratory Questionnaire (SGRQ)

Table 18 shows the differences in scores on the quality of life measure, the St. George's Respiratory Questionnaire (SGRQ). The differences in SGRQ scores for mepolizumab (100mg SC group) vs. placebo in MENSA were -7.0 (95% CI -10.2, -3.8) for the ITT population; -10.0 (95% CI -15.5, -4.5) for the GSK PP; -12.8 (95% CI -19.9, -5.8) for the GSK PP excl. c mOCS; and -1.2 (95% CI -10.8, 8.4) in the stable mOCS population. Data from MENSA for the mepolizumab 75mg IV group were similar. In SIRIUS, improvements for mepolizumab over placebo were approximately 5 to 6 units in all groups. SGRQ was not an endpoint in DREAM.

The CS states that the minimal clinically important difference (MCID) for SGRQ is 4 units (CS p87) and the differences in MENSA and SIRIUS range from 5 to 13 units in all groups, with the exception of the stable mOCS population in MENSA in which the improvement was only 1 to 3 units. The placebo groups improved from baseline by approximately 9 units and the mepolizumab groups by approximately 15-21 units, therefore the improvement was approximately two-fold greater in the mepolizumab than in the placebo groups.

Asthma Control Questionnaire (ACQ)

Table 19 shows the differences in scores on the quality of life measure, the Asthma Control Questionnaire (ACQ). The differences in ACQ scores between mepolizumab (100mg SC and 75mg IV groups combined) vs. placebo, meta-analysed across MENSA and DREAM, were -0.34 (95% CI -0.48, -0.20) for the ITT population; -0.56 (95% CI -0.79, -0.33) for the GSK PP; -0.76 (95% CI -1.05, -0.47) for the GSK PP excl. stable mOCS; and -0.30 (95% CI -0.71, 0.10) in the stable mOCS population. The CS states that the MCID for ACQ is 0.5 units (CS p88), in which case, the ITT population would almost achieve clinical importance and the GSK population (but not the stable mOCS population) would show clinical importance. The placebo groups improved from baseline by approximately 0.3 to 0.5 units and the mepolizumab groups by

approximately 0.9 to 1.2 units, therefore the improvement was approximately two-to-three-fold greater in the mepolizumab than in the placebo groups.

Asthma Quality of Life Questionnaire (AQLQ)

Data for DREAM for the Asthma Quality of Life Questionnaire (AQLQ) is shown in Table 20. The differences in AQLQ scores between mepolizumab (75mg IV) vs. placebo were 0.08 (95% CI -0.16, 0.32) for the ITT population; 0.17 (95% CI -0.23, 0.57) for the GSK PP; and 0.38 (95% CI -0.14, 0.90) for the GSK PP excl. stable mOCS; no data were provided for the stable mOCS population. This outcome was not an endpoint in MENSA or SIRIUS. The MCID for the AQLQ is approximately 0.5 units;[36] therefore, none of the populations showed a clinically important difference on the AQLQ.

EQ-5D

Data for DREAM for the EQ-5D is shown in Table 21. This outcome was not an endpoint in MENSA or SIRIUS.

Table 17: Results for pre-bronchodilator FEV_1 (ml)

	ITT				GSK PP				GSK PP excl. stable mOCS				Stable mOCS			
	Placebo	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**
	MENSA															
N	189	192	188	380	59	76	59		40	53	43					
LS mean (SE)	1907 (31.4)	2005 (31.1)	2007 (31.5)	2006 (22.1)	1844 (59.1)	1960 (52.8)	1975 (59.3)		1855 (75.4)	1962 (67.3)	2002 (72.9)					
LS mean change (SE)	86 (31.4)	183 (31.1)	186 (31.5)	184 (22.1)	118 (59.1)	234 (52.8)	249 (59.3)		114 (75.4)	221 (67.3)	261 (72.9)					
Difference (mepo-pbo)		**98**	**100**	**99**		**116**	**131**	Not provided		**107**	**148**	Not provided		Not requested	Not requested	Not requested
95% CI		(11, 184)	(13, 187)	(23, 174)		(-41,272)	(-35,296)			(-95,309)	(-59,355)					
p-value		0.028	0.025	0.010		0.147	0.120			0.295	0.160					
	DREAM															
N	154		152	152												
LS mean (SE)	2021 (37.6)		2024 (37.6)	2024 (37.6)												
LS mean change (SE)	139 (37.6)		142 (37.6)	142 (37.6)												
Difference (mepo-pbo)			**3**	**3**			Not provided	Not provided			Not provided	Not provided			Not requested	Not requested
95% CI			(-97, 102)	(-97, 102)												
p-value			0.958	0.958												
	SIRIUS															
N	62	66		66	46	52		52								
LS mean (SE)	1955 (56.5)	2070 (55.1)		2070 (55.1)	1896 (66.2)	2036 (62.3)		2036 (62.3)								
LS mean change (SE)	-4 (56.5)	111 (55.1)		111 (55.1)	17 (66.2)	157 (62.3)		157 (62.3)								
Difference (mepo-pbo)		**114**		**114**		**140**		**140**		Not requested		Not requested		Not requested		Not requested
95% CI		(-42, 271)		(-42, 271)		(-41, 321)		(-41, 321)								
p-value		0.151		0.151		0.129		0.129								
	Meta-analyses not provided in the CS or requested by the ERG															

Analysis performed using mixed model repeated measures with covariates of baseline, region, treatment and visit, plus interaction terms for visit by baseline and visit by treatment group. CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; IV = intravenous; ml = millilitres; mOCS = maintenance oral corticosteroids; SC = subcutaneous; SE = standard error

Table 18: Results for St. George's Respiratory Questionnaire (SGRQ)

	ITT				GSK PP				GSK PP excl. stable mOCS				Stable mOCS			
	Placebo	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**
	MENSA															
N	177	184	174		59	75	58		40	53	42		19	22	16	
LS mean (SE)	37.7 (1.16)	30.7 (1.13)	31.2 (1.16)		41.3 (2.08)	31.3 (1.86)	33.4 (2.12)		42.4 (2.64)	29.5 (2.32)	32.5 (2.59)		38.1 (3.38)	36.9 (3.17)	35.4 (3.69)	
LS mean change (SE)	-9.0 (1.16)	-16.0 (1.13)	-15.4 (1.16)		-8.7 (2.08)	-18.7 (1.86)	-16.6 (2.12)		-8.2 (2.64)	-21.1 (2.32)	-18.1 (2.59)		-10.7 (3.38)	-11.9 (3.17)	-13.4 (3.69)	
Difference (mepo-pbo)		**-7.0**	**-6.4**	Not provided		**-10.00**	**-7.90**	Not provided		**-12.8**	**-9.9**	Not provided		**-1.2**	**-2.7**	Not provided
95% CI		-10.2, -3.8	-9.7, -3.2			-15.5,-4.5	-13.8,-2.0			-19.9,-5.8	-17.2,-2.5			-10.8, 8.4	-12.8, 7.5	
p-value		<0.001	<0.001			<0.001	0.008			<0.001	0.009			0.803	0.602	
	DREAM															
	Not an endpoint in DREAM															
	SIRIUS															
N	61	65		65	45	51		51	15	22		22	30	29		29
LS mean (SE)	44.3 (1.73)	38.5 (1.68)		38.5 (1.68)	43.8 (2.17)	38.2 (2.03)		38.2 (2.03)	44.9 (4.76)	39.9 (3.91)		39.9 (3.91)	43.0 (2.24)	37.2 (2.28)		37.2 (2.28)
LS mean change (SE)	-3.1 (1.73)	-8.8 (1.68)		-8.8 (1.68)	-3.5 (2.17)	-9.1 (2.03)		-9.1 (2.03)	-6.5 (4.76)	-11.5 (3.91)		-11.5 (3.91)	-1.7 (2.24)	-7.5 (2.28)		-7.5 (2.28)
Difference (mepo-pbo)		**-5.8**		**-5.8**		**-5.6**		**-5.6**		**-5.0**		**-5.0**		**-5.8**		**-5.8**
95% CI		-10.6, -1.0		-10.6, -1.0		-11.6, 0.4		-11.6, 0.4		-17.7, 7.7		-17.7, 7.7		-12.3, 0.7		-12.3, 0.7
p-value		0.019		0.019		0.066		0.066		0.427		0.427		0.08		0.08
	MENSA & SIRIUS meta-analysis															
N					104			126	55			75	49			51
Difference (mepo-pbo)			Not possible – different covariates				Not requested	**-8.0**			Not requested	**-10.9**			Not requested	**-4.3**
95% CI								-12.0, -3.9				-17.0, -4.8				-9.6, 0.9
p-value								<0.001				<0.001				0.106

Only subjects with a Baseline and Week 32 assessment are included in the analysis. Analysis performed using analysis of covariance with covariates of baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), baseline % predicted FEV_1, and treatment. CI = confidence interval; GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; IV = intravenous; mOCS = maintenance oral corticosteroids; SC = subcutaneous; SE = standard error; SGRQ = St. George's Respiratory Questionnaire

Table 19: Results for Asthma Control Questionnaire (ACQ)

	ITT				GSK PP				GSK PP excl. stable mOCS				Stable mOCS			
	Placebo	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**
	MENSA															
N	170	173	161	334	58	73	57		40	51	41		18	22	16	
LS mean (SE)	1.70 (0.069)	1.26 (0.068)	1.28 (0.070)	1.27 (0.049)	1.97 (0.113)	1.18 (0.102)	1.43 (0.114)		2.06 (0.139)	1.10 (0.125)	1.34 (0.136)		1.86 (0.196)	1.38 (0.180)	1.56 (0.208)	
LS mean change (SE)	-0.50 (0.069)	-0.94 (0.068)	-0.92 (0.070)	-0.93 (0.049)	-0.38 (0.113)	-1.17 (0.102)	-0.92 (0.114)		-0.27 (0.139)	-1.23 (0.125)	-0.98 (0.136)		-0.55 (0.196)	-1.04 (0.180)	-0.85 (0.208)	
Difference (mepo-pbo)		**-0.44**	**-0.42**	**-0.43**		**-0.79**	**-0.54**	Not provided		**-0.96**	**-0.72**	Not provided		**-0.48**	**-0.3**	Not provided
95% CI		-0.63, -0.25	-0.61, -0.23	-0.59, -0.26		-1.09,-0.49	-0.86,-0.23			-1.33,-0.59	-1.10,-0.33			-1.03, 0.07	-0.87, 0.28	
p-value		<0.001	<0.001	<0.001		<0.001	<0.001			<0.001	<0.001			0.083	0.304	
	DREAM															
N	121		127	127	43		45	45	23		32	32	20		13	13
LS mean (SE)	1.72 (0.087)		1.56 (0.087)	1.56 (0.087)	1.94 (0.176)		1.76 (0.178)	1.76 (0.178)	2.18 (0.246)		1.71 (0.221)	1.71 (0.221)	1.90 (0.268)		1.91 (0.341)	1.91 (0.341)
LS mean change (SE)	-0.59 (0.087)		-0.75 (0.087)	-0.75 (0.087)	-0.55 (0.176)		-0.73 (0.178)	-0.73 (0.178)	-0.33 (0.246)		-0.80 (0.221)	-0.80 (0.221)	-0.56 (0.268)		-0.55 (0.341)	-0.55 (0.341)
Difference (mepo-pbo)			**-0.16**	**-0.16**			**-0.17**	**-0.17**			**-0.47**	**-0.47**			**0.01**	**0.01**
95% CI			-0.39, 0.07	-0.39, 0.07			-0.65, 0.30	-0.65, 0.30			-1.09 0.16	-1.09 0.16			-0.81, 0.84	-0.81, 0.84
p-value			0.183	0.183			0.473	0.473			0.142	0.142			0.972	0.972
	SIRIUS															
N	53	58		58	42	45		45	13	19		19				
LS mean (SE)	1.98 (0.128)	1.46 (0.126)		1.46 (0.126)	2.08 (0.150)	1.43 (0.143)		1.43 (0.143)	2.61 (0.311)	1.73 (0.259)		1.73 (0.259)	Analysis did not converge			
LS mean change (SE)	-0.09 (0.128)	-0.61 (0.126)		-0.61 (0.126)	-0.04 (0.150)	-0.69 (0.143)		-0.69 (0.143)	0.22 (0.311)	-0.66 (0.259)		-0.66 (0.259)				
Difference (mepo-pbo)		**-0.52**		**-0.52**		**-0.65**		**-0.65**		**-0.88**		**-0.88**				
95% CI		-0.87, -0.17		-0.87, -0.17		-1.06, -0.24		-1.06, -0.24		-1.71, -0.05		-1.71, -0.05				
p-value		0.004		0.004		0.002		0.002		0.038		0.038				
	DREAM & MENSA meta-analysis															
N	298			465	119			191	76			137	43			54
Difference (mepo-pbo)				**-0.34**				**-0.56**				**-0.76**				**-0.30**

	ITT				GSK PP				GSK PP excl. stable mOCS				Stable mOCS			
	Placebo	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**
95% CI				-0.48, -0.20				-0.79, -0.33				-1.05, -0.47				-0.71, 0.10
p-value				<0.001				<0.001				<0.001				0.144
	DREAM & MENSA & SIRIUS meta-analysis															
N					168			251	92			163	76			88
Difference (mepo-pbo)			Not possible – different covariates					**-0.58**				**-0.78**				**-0.43**
95% CI								-0.79, -0.38				-1.05, -0.50				-0.75, -0.12
p-value								<0.001				<0.001				**0.007**

Analysis performed using mixed model repeated measures with covariates of baseline, region, baseline maintenance OCS therapy (OCS vs. no OCS), baseline % predicted FEV_1, treatment, and visit, plus interaction terms for visit by baseline and visit by treatment group. ACQ = Asthma Control Questionnaire; CI = confidence interval; GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; IV = intravenous; mOCS = maintenance oral corticosteroids; SC = subcutaneous; SE = standard error

Table 20: Results for Asthma Quality of Life Questionnaire (AQLQ)

	ITT		GSK PP		GSK PP excl. stable mOCS		Stable mOCS	
	Placebo	Mepo 75mg IV	Placebo	Mepo 75mg IV	Placebo	Mepo 75mg IV	Placebo	Mepo 75mg IV
	Not an endpoint in MENSA or SIRIUS							
	DREAM							
n	123	128	44	46	23	33		
LS mean (SE)	4.92 (0.090)	5.00 (0.089)	4.87 (0.149)	5.03 (0.148	4.63 (0.209)	5.01 (0.181)		
LS mean change (SE)	0.71 (0.090)	0.80 (0.089)	0.64 (0.149)	0.81 (0.148)	0.47 (0.209)	0.85 (0.181)		
Difference (mepo-pbo)		**0.08**		**0.17**		**0.38**		Not provided
95% CI		-0.16, 0.32		-0.23, 0.57		-0.14, 0.90		
p-value		0.501		0.413		0.151		

AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; IV = intravenous; mOCS = maintenance oral corticosteroids; SE = standard error

Table 21: Results for EQ-5D

		ITT		GSK PP		GSK PP excl. stable mOCS		Stable mOCS	
		Placebo	Mepo 75mg IV	Placebo	Mepo 75mg IV	Placebo	Mepo 75mg IV	Placebo	Mepo 75mg IV
		Not an endpoint in MENSA or SIRIUS							
		DREAM							
Week 52 Index score	n	127	130	45	46	25	32	20	14
	Mean (SD)	0.82 (0.214)	0.81 (0.209)	0.78 (0.221)	0.82 (0.202)	0.79 (0.154)	0.81 (0.224)	0.75 (0.287)	0.86 (0.141)
	Median	0.85	0.81	0.80	0.80	0.80	0.80	0.82	0.83
	Min, Max	-0.2, 1.0	-0.2, 1.0	0.1, 1.0	-0.2, 1.0	0.5 1.0	-0.2, 1.0	0.1, 1.0	0.6, 1.0
Week 52 Change from Baseline	n	127	130	45	46	25	32	20	14
	Mean (SD)	0.07 (0.221)	0.08 (0.252)	-0.03 (0.194)	0.05 (0.268)	-0.05 (0.146)	0.04 (0.302)	0.00 (0.243)	0.07 (0.179)
	Median	0.04	0.03	0.00	0.05	0.00	0.05	0	0.03
	Min, Max	-0.6, 0.8	-1.0, 1.2	-0.5, 0.4	-1.0, 0.6	-0.3, 0.3	-1.0, 0.6	-0.5, 0.4	-0.3, 0.3

EQ-5D = EuroQol 5 Dimensions; GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; IV = intravenous; mOCS = maintenance oral corticosteroids; SD = standard deviation

OCS dose reduction during weeks 20-24 (SIRIUS)

The primary endpoint of the SIRIUS trial was the percentage reduction in OCS dose during weeks 20-24 compared to the baseline dose, whilst maintaining asthma control. This was categorised as follows: 90% to 100% reduction; 75% to <90% reduction; 50% to <75% reduction; >0% to <50% reduction; or no reduction, lack of asthma control, or withdrawal from treatment.

Table 22 shows the number and percent of participants achieving the different levels of OCS reduction. Results are presents as odds ratios (ORs) for mepolizumab vs. placebo as follows: OR=2.39 (95% CI 1.25, 4.56) in the ITT population; OR=1.81 (95% CI 0.86, 3.79) for the GSK PP; OR=2.75 (95% CI 0.72, 10.59) for the GSK PP excl. stable mOCS. In the two GSK populations, this result favours mepolizumab but does not reach statistical significance, though numbers in these

populations are relatively small. These data were not provided in the CS, or requested by the ERG, for the stable mOCS population.

Absolute differences between mepolizumab and placebo for the proportion achieving a reduction in OCS dose whilst maintaining asthma control were 20% in the ITT population, 13% in the GSK PP, and 26% in the GSK PP excl. stable mOCS.

Table 22: Percent reduction of OCS dose during weeks 20-24 (SIRIUS primary endpoint)

Percent reduction of OCS dose in weeks 20-24 vs. baseline dose while maintaining asthma control	Number (%) Subjects					
	ITT		GSK PP		GSK PP excl. stable mOCS	
	Placebo	Mepo 100mg SC	Placebo	Mepo 100mg SC	Placebo	Mepo 100mg SC
N	66	69	48	54	15	22
90% - 100%	7(11)	16 (23)	6 (13)	10 (19)	2 (13)	3 (14)
75% - <90%	5 (8)	12 (17)	5 (10)	9 (17)	1 (7)	5 (23)
50% - <75%	10 (15)	9 (13)	7 (15)	7 (13)	1 (7)	3 14)
>0% - <50%	7 (11)	7 (10)	4 (8)	6 (11)	1 (7)	2 (9)
No change or any increase or lack of asthma control or withdrawal from treatment	37 (56)	25 (36)	26 (54)	22 (41)	10 (67)	9 (41)
OR vs. placebo	-	**2.39**	-	**1.81**	-	**2.75**
95% CI	-	1.25, 4.56	-	(0.86, 3.79)	-	0.72, 10.59
p-value	-	0.008	-	0.115	-	0.140

Analysed using a proportional odds model (multinomial (ordered) logistic generalised linear model), with terms for treatment group, region, baseline maintenance oral corticosteroids stratum (OCS use <5 years vs. OCS use ≥5 years) and baseline OCS dose (optimised dose). CI = confidence interval; GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; mOCS = maintenance oral corticosteroids; SC = subcutaneous

Secondary endpoints of reduction in OCS dose during weeks 20-24 (SIRIUS)

A range of secondary endpoints for OCS dose reduction were also reported for SIRIUS, at weeks 20-24 compared with baseline (Table 23). In the GSK PP, a reduction in OCS dose of at least 50% was observed in 48% of patients (mepolizumab) vs. 38% (placebo), giving an OR of 1.60 (95% CI 0.70, 3.64) and an absolute difference of 10%. A reduction in OCS dose to ≤5 mg was observed in 50% of patients (mepolizumab) vs. 40% (placebo), with an OR of 1.64 (95% CI 0.68, 3.93) and an absolute difference of 10%. A complete (i.e. 100%) reduction in OCS dose was observed in 13% (mepolizumab) vs. 8% (placebo), with an OR of 1.35 (95% CI 0.32, 5.78) and an absolute difference of 5%. Results were not significant, though numbers in this population were relatively small.

ORs were slightly more favourable in the ITT population than the GSK PP, and were generally statistically significant in the ITT population (Table 23). Results in the GSK PP excl. stable mOCS were also slightly more favourable than in the GSK PP.

Table 23: Secondary endpoints of reduction in OCS dose during weeks 20-24 (SIRIUS)

	Number (%) Subjects					
	ITT		GSK PP		GSK PP excl. stable mOCS	
	Placebo	Mepo 100mg SC	Placebo	Mepo 100mg SC	Placebo	Mepo 100mg SC
N for all secondary measures	66	69	48	54	15	22
≥50% Reduction in Daily OCS Dose, n (%)						
50% to 100%	22 (33)	37 (54)	18 (38)	26 (48)	4 (27)	11 (50)
<50%, no decrease in OCS, lack of asthma control, or withdrawal from treatment	44 (67)	32 (46)	30 (63)	28 (52)	11 (73)	11(50)
OR vs. placebo	**-**	**2.26**	**-**	**1.60**	**-**	**2.93**
95% CI	-	1.10, 4.65	-	(0.70, 3.64)	-	0.68, 12.53
p-value	-	0.027	-	0.266	-	0.147
Reduction in Daily OCS Dose to ≤5 mg, n (%)						
Reduction to ≤5 mg	21 (32)	37 (54)	19 (40)	27 (50)	5 (33)	11 (50)
Reduction to >5 mg, lack of asthma control, or withdrawal from treatment	45 (68)	32 (46)	29 (60)	27 (50)	10 (67)	11 (50)
OR vs. placebo	**-**	**2.45**	**-**	**1.64**	**-**	**2.68**
95% CI	-	1.12, 5.37	-	(0.68, 3.93)	-	0.52, 13.70
p-value	-	0.025	-	0.268	-	0.237
Total Reduction of OCS Dose, n (%)						
Total (100%) reduction (0 mg)	5 (8)	10 (14)	4 (8)	7 (13)	1 (7)	2 (9)
OCS taken, lack of asthma control, or withdrawal from treatment	61 (92)	59 (86)	44 (92)	47 (87)	14 (93)	20 (91)
OR vs. placebo	**-**	**1.67**	**-**	**1.35**	Insufficient events	
95% CI	-	0.49, 5.75	-	(0.32, 5.78)	-	-
p-value	-	0.414	-	0.684	-	-
Median Percentage Reduction in Daily OCS Dose						
Median (%)	0.0	50.0	0.0	36.5	0.0	48.1
95% CI of the median	-20.0, 33.3	20.0, 75.0	(0.0, 50.0)	(0.0, 66.7)	-270, 66.7	0.0, 80.0
Median difference	**-**	**-30.0**	**-**	**-14.3**	**-**	**33.3**
95% CI of the median difference	-	-66.7, 0.0	-	(-50.0, 0.0)	-	-11.1, 90.1
p-value	-	0.007	-	0.162	-	0.236

Analysed using a binary logistic regression model with terms for treatment group, region, baseline maintenance oral corticosteroids stratum (OCS use <5 years vs. OCS use ≥5 years) and baseline OCS dose (optimised dose). CI = confidence interval; GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; mOCS = maintenance oral corticosteroids; SC = subcutaneous

4.2.3.2 Subgroup analyses

Post hoc subgroup analyses and modelling were undertaken by the company. Statistical methods are described in Section 4.2.2.4. These analyses were used as the basis for identifying the two GSK proposed populations. Subgroup analyses are described in the CS (p76-83 and p101-111). As noted in Section 3.1.3, the four relevant sub-populations are as follows:

- **Intention-to-treat (ITT) population:** All trial patients who were randomised and received at least one dose of study medication; this is actually a form of modified ITT (mITT) but this population is referred to in the ERG report as the ITT population for consistency with the CS.
- **GSK proposed population (GSK PP):** Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/µl at initiation of treatment; and ≥4 exacerbations in the previous year and/or dependency on mOCS (regardless of exacerbations in previous year).
- **GSK PP excluding mOCS users with <4 exacerbations (GSK PP excl. stable mOCS):** Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/µl at initiation of treatment; and ≥4 exacerbations in the previous year.
- **mOCS users with <4 exacerbations (stable mOCS):** Adult severe refractory eosinophilic asthma patients with a blood eosinophil count of ≥150 cells/µl at initiation of treatment; and <4 exacerbations in the previous year.

Overview of main findings from subgroup analyses

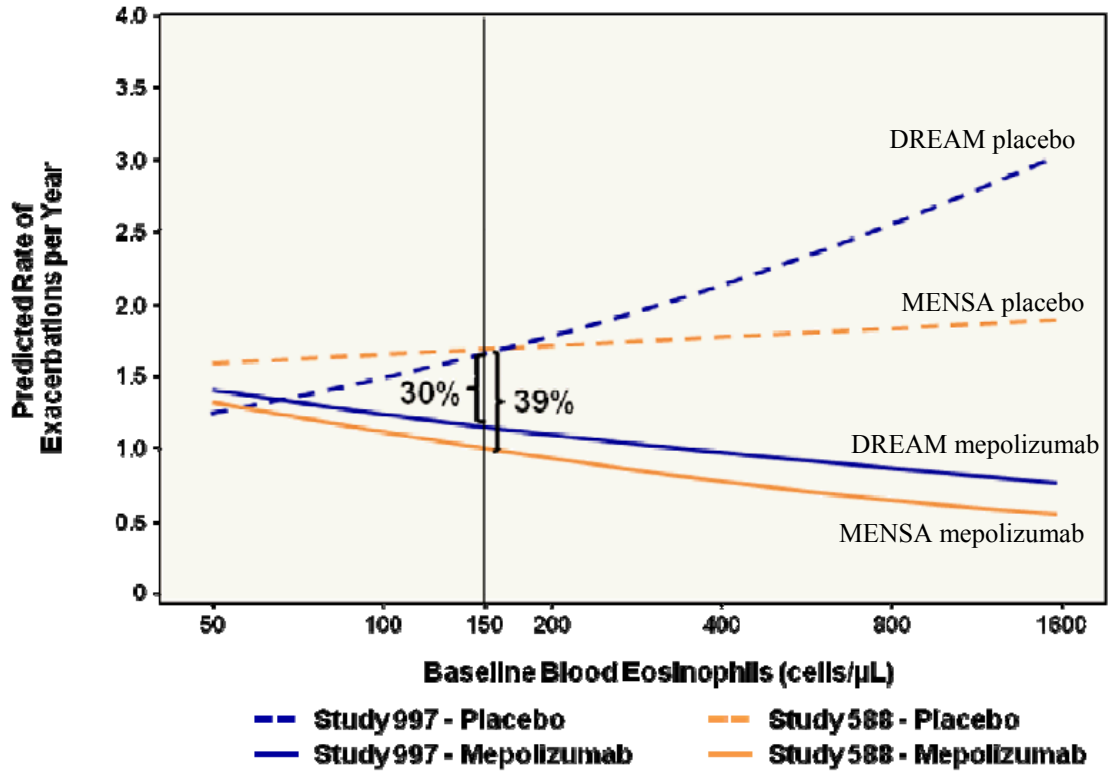
Multivariate modelling of DREAM data showed that the covariates influencing the number of exacerbations (as selected using backwards selection at the 5% significance level) were: treatment, number of exacerbations in the year prior to baseline, randomisation stratum (stable OCS use at baseline or not), region and gender (DREAM CSR p1559). Blood eosinophil count was identified as the strongest predictor of treatment response (test of interaction with treatment, p=0.0001) with number of exacerbations in the year prior to baseline also potentially predictive of treatment response (p=0.0009). Multivariate modelling in MENSA showed that the covariates influencing the number of exacerbations were: treatment; blood eosinophil counts at screening; exacerbations in the year prior to screening; and baseline maintenance oral glucocorticosteroid use. Blood eosinophil count was the only covariate identified as a predictor of treatment response (interaction term for blood eosinophils p<0.05).

Further subgroup analysis of the DREAM data identified several variables with potentially significant interactions with treatment group: number of previous exacerbations (p=0.014), baseline blood eosinophil group (p=0.002), region (p=0.010) and baseline total IgE concentration at baseline (p=0.021). For the latter two covariates it is noted by the ERG that the observed effect may be due to the potentially confounding effect of other variables and that multivariate modelling of response did not show any differential effect of mepolizumab according to these covariates (DREAM CSR p67-81). Subgroups based on the number of previous exacerbations and baseline blood eosinophil group are discussed in further detail below.

Baseline blood eosinophil threshold

The company defined a clinically meaningful reduction in exacerbations (for mepolizumab vs. placebo) as a reduction of at least 30%, based on other literature of add-on therapies in asthma[37-39] indicating that a reduction of 20 to 25% is clinically relevant (CS p76). A *post hoc* modelling analysis of data from the DREAM trial showed that patients with a blood eosinophil count of ≥150 cells/μL at initiation of treatment had a ≥30% reduction in rate of exacerbations for mepolizumab vs. placebo (Figure 1, reproduced from CS p77). A *post hoc* analysis of data from the MENSA trial showed a 39% reduction in rate of exacerbations for mepolizumab vs. placebo for patients with a blood eosinophil threshold of ≥150 cells/μL.

Figure 1: Predicted rate of exacerbations by baseline blood eosinophil count (DREAM and MENSA, CS Figure 7)



The ERG considers that the justification of the derived threshold should be interpreted with caution. Figure 1 suggests that, for the placebo group in DREAM, the predicted rate of exacerbations increases notably as baseline blood eosinophils increases, whilst for the mepolizumab group, the predicted rate of exacerbations decreases. This phenomenon is also seen in the MENSA trial. No clinical justification is provided for why, in the treatment group, patients with higher baseline blood eosinophils (indicative of more severe asthma) would have a lower predicted rate of exacerbations.

Figure 1 does not convey the uncertainty in the relationship between baseline blood eosinophils and rate of exacerbations, or a confidence interval associated with this 30% reduction. Whilst the interaction term was found to be statistically significant (p=0.0001), the main effect of the blood eosinophils was not found to be statistically significant at the 5% level and so there is likely to be considerable uncertainty associated with the illustrated predicted rates.

The number of previous exacerbations is also shown to be prognostic of treatment effect, and so the blood eosinophil threshold required to obtain a 30% reduction in the rate of exacerbation will vary according to this covariate. In response to a request from the ERG for clarification, the company provided relative cut-offs separately according to the number of previous exacerbations (Table 24). Using data from DREAM, for patients with 2 exacerbations (n=286, 46% of total) a threshold of between 350 and 400 cells/ µL would be required to achieve the specified reduction in rate. For patients with ≥4 exacerbations (representative of the GSK PP) the reported threshold is <50 cells/ µL.

Table 24: Eosinophil levels that predict a 30% reduction in exacerbations conditional on exacerbations in the previous year (clarification response A15)

Exacerbations in previous year	Eosinophil level that predicts a 30% reduction	
	Study DREAM	Study MENSA
2 exacerbations	Between 350 and 400 cells/ µL	Between 100 and 150 cells/ µL
3 exacerbations	Between 100 and 150 cells/ µL	Between 50 and 100 cells/ µL
≥4 exacerbations	<50 cells/µL	Between 50 and 100 cells/ µL

The rate of exacerbations according to blood eosinophil level in MENSA is shown in Table 25 (adapted from CS p103). This compares two different options for a blood eosinophil threshold: ≥150/µL at screening, or ≥300/µL in the previous 12 months. Clinical advisors to the ERG advised that a threshold of 300 cells/µL would appear more appropriate since 150 cells/µL was a relatively low count which was within the normal range, and that a threshold observed anytime in the previous 12 months would seem more appropriate than one observed exactly at the point of screening since eosinophil level can fluctuate.

Patients with ≥150/µL at screening had greater reduction in exacerbations for mepolizumab vs. placebo (RR=0.46 and 0.38 for 75mg IV and 100mg SC respectively) than patients with <150/µL

(RR=0.94 and 0.91). The company use these results as the basis for focussing on patients with ≥150/μL at screening.

However, the results observed for subgroups based on a threshold of ≥300/μL in the previous 12 months were not intuitive for the following two reasons:

1) Exacerbation rates in the placebo groups were lower for patients with ≥300/μL in the previous 12 months compared with patients with <300/μL (1.64 vs. 1.89), and
2) Patients with ≥300/μL in the previous 12 months had a smaller reduction in exacerbations for mepolizumab vs. placebo (RR=0.69 and 0.57) than patients with <300/μL (RR=0.27 and 0.27), which is not intuitive.

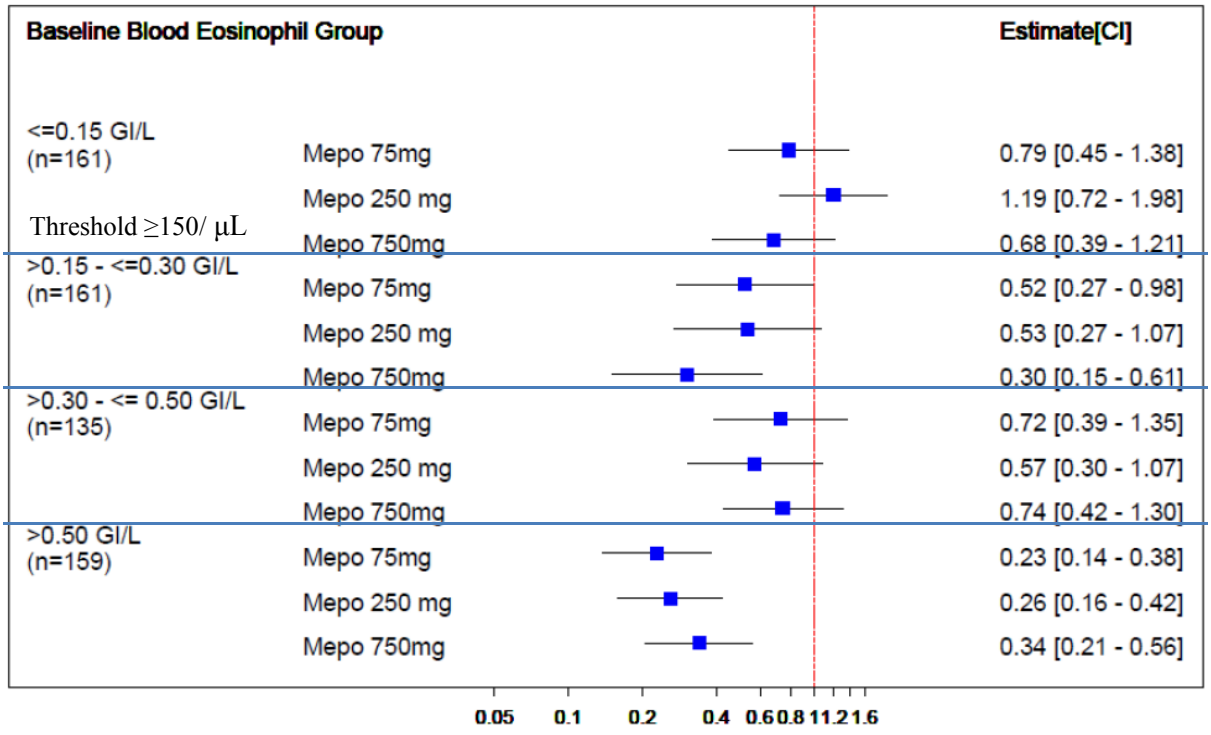
Table 25: Analysis of rate of clinically significant exacerbations by blood eosinophil criteria (MENSA, adapted from CS p103 Table 44)

Blood eosinophil inclusion criteria group	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
Criterion: ≥300/μL in the previous 12 months			
<300/μL in the previous 12 months			
N Exacerbation rate/year	70 1.89	61 0.51	48 0.50
RR (mepolizumab/placebo) 95% CI		**0.27** 0.15, 0.51	**0.27** 0.14, 0.52
≥300/μL in the previous 12 months			
N Exacerbation rate/year	121 1.64	130 1.13	146 0.94
RR (mepolizumab/placebo) 95% CI		**0.69** 0.49, 0.98	**0.57** 0.41, 0.80
Criterion: ≥150/μL at screening[1]			
<150/μL at screening			
N Exacerbation rate/year	21 1.31	30 1.23	35 1.20
RR (mepolizumab/placebo) 95% CI		**0.94** 0.43, 2.07	**0.91** 0.44, 1.90
≥150/μL at screening			
N Exacerbation rate/year	167 1.75	155 0.81	155 0.67
RR (mepolizumab/placebo) 95% CI		**0.46** 0.33, 0.64	**0.38** 0.27, 0.53

1. Thirteen subjects are not shown in this analysis due to having no eosinophil count measured at screening. CI = confidence interval; IV = intravenous; SC = subcutaneous

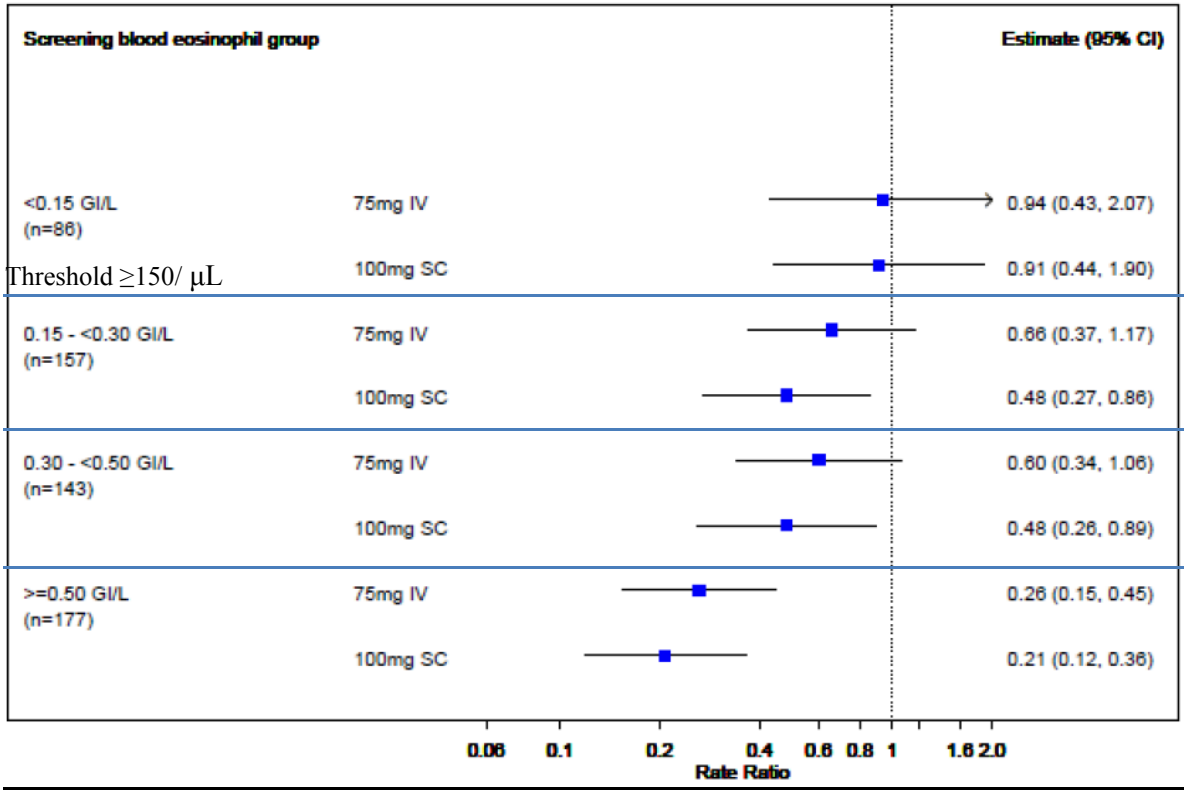
Figure 2 (DREAM, CS p105) and Figure 3 (MENSA, CS p106) illustrate the RRs for exacerbations (mepolizumab vs. placebo) for patients grouped by blood eosinophil count. For each figure, the top horizontal line indicates the ≥150/µL threshold. It can be seen that in both studies, the RR for exacerbations broadly improves (decreases) as the baseline eosinophil count increases. However, the use of a ≥150/µL cut-off is not clear-cut since (for example) patients with an eosinophil count of 300-500/µL actually seem to have a worse (higher) RR than patients with 150-300/µL. For DREAM, there was a statistically significant interaction between baseline blood eosinophil group and treatment effect (p=0.002), however it is worth noting that this relates to the four presented subgroups, rather than the utilised ≥150/µL or <150/µL cut-off.

Figure 2: Rate ratios for clinically significant exacerbations by baseline blood eosinophils (DREAM, CS Figure 12)



CI = confidence interval

Figure 3: Rate ratios for clinically significant exacerbations by screening blood eosinophils (MENSA, CS Figure 13)



CI = confidence interval

The company undertook predictive modelling for both studies to investigate the relationship between baseline blood eosinophils and history of exacerbations with the exacerbation rate. Results are shown for DREAM (Figure 4, CS p104) and MENSA (
Figure 5, CS p80).

Figure 4: Predictive modelling of exacerbation rate based on baseline blood eosinophil count, history of exacerbations and treatment with mepolizumab or placebo (DREAM, CS Figure 11)

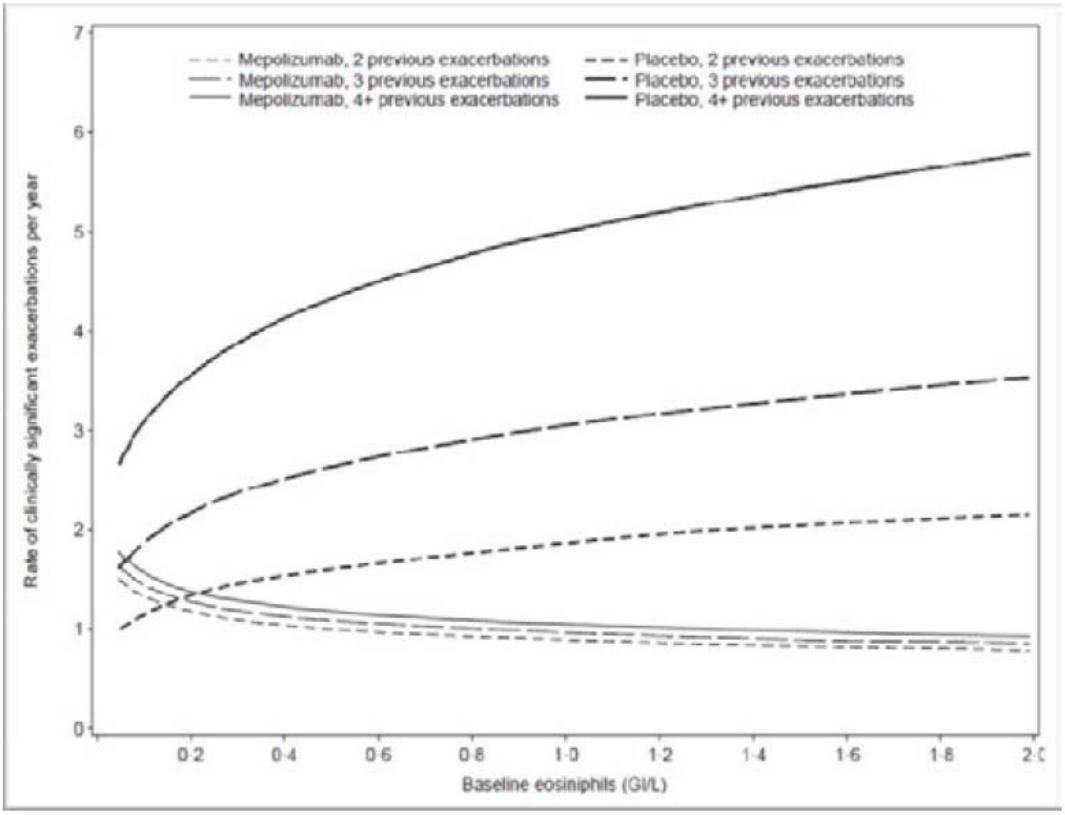
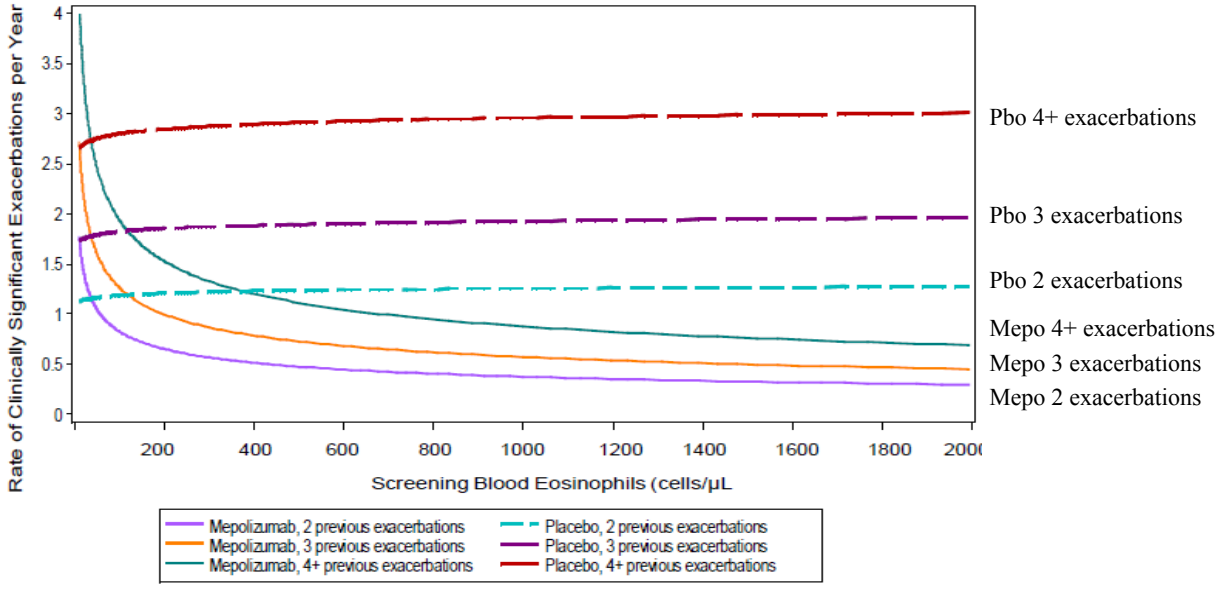


Figure 5: Predictive modelling of exacerbation rate based on screening blood eosinophil count, history of exacerbations and treatment with mepolizumab or placebo (MENSA, CS Figure 8)



CS states: Figure adapted from Ortega *et al*. 2014. Mepo = mepolizumab; Pbo = placebo

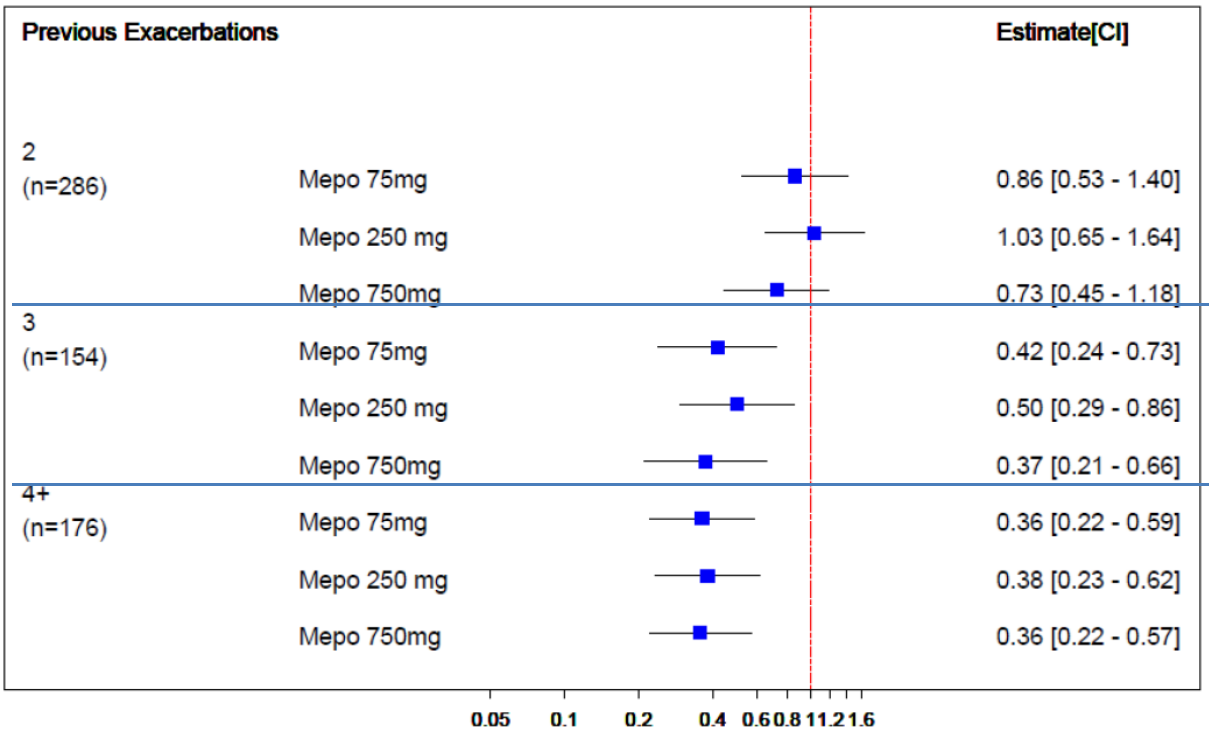
Previous exacerbations threshold

For DREAM, the CS states that a planned subgroup analysis showed greater decreases in exacerbations in the mepolizumab groups (vs. placebo) in subjects who had previously experienced more exacerbations (Figure 6, CS p108). Previous exacerbations are defined as exacerbations requiring systemic corticosteroids (or for subjects on mOCS, a two-fold or greater dose increase). It should be noted that this is different to the definition of clinically significant exacerbations used in the trials, which includes exacerbations requiring systemic corticosteroids and/or hospitalisations or ED visits.

The CS states that the interaction between the number of previous exacerbations and treatment group was potentially significant (p=0.014); this indicates that there was a potentially significant difference in exacerbation reduction for patients according to the number of prior exacerbations. For patients receiving mepolizumab 75mg, the RRs for exacerbations vs. placebo were 0.86 (2 previous exacerbations); 0.42 (3 previous exacerbations); and 0.36 (4 previous exacerbations). However, although the RRs appear more favourable for subgroups with 3 or ≥4 than for 2 previous exacerbations, there appears to be little difference in RR between those with 3 and ≥4 previous exacerbations (Figure 6).

For MENSA, exacerbation rates according to previous exacerbation history are shown in Table 26 (CS p80). The rate of exacerbations in the placebo arm increases as the number of exacerbations in the previous year increases: from a rate of 1.09 for 2 previous exacerbations rising to 3.22 for ≥4 previous exacerbations. For the mepolizumab 75mg IV and 100mg SC groups, the RRs vs. placebo were 0.57 and 0.53 (2 previous exacerbations); 0.56 and 0.30 (3 previous exacerbations); and 0.40 and 0.44 (4 previous exacerbations). The combination of these data indicate that the greatest absolute number of exacerbations prevented would be in the groups with 4 or more previous exacerbations.

Figure 6: Rate ratios for clinically significant exacerbations by previous exacerbations: ratio to placebo (DREAM, CS Figure 14)



NB: One subject in the placebo group and one subject in the mepolizumab 250mg group had fewer than two exacerbations in the 12 months prior to screening and were defined as protocol violators. CI = confidence interval

Table 26: Rate ratios for clinically significant exacerbations by previous exacerbations (MENSA, CS Table 22)

Previous exacerbation group	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
Previous exacerbations: 2			
N Exacerbation rate/year	90 1.09	82 0.61	74 0.58
Rate ratio (mepolizumab/placebo) 95% CI		**0.57** 0.33, 0.96	**0.53** 0.30, 0.94
Previous exacerbations: 3			
N Exacerbation rate/year	46 1.63	47 0.91	48 0.48
Rate ratio (mepolizumab/placebo) 95% CI		**0.56** 0.33, 0.94	**0.30** 0.16, 0.55
Previous exacerbations: ≥4			
N Exacerbation rate/year	55 3.22	62 1.29	72 1.43
Rate ratio (mepolizumab/placebo) 95% CI		**0.40** 0.25, 0.64	**0.44** 0.29, 0.69

Analysis of number of exacerbations performed using separate negative binomial models for each subgroup presented with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, exacerbations in the year prior to the study (as an ordinal variable) and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. For this analysis, Canada is combined with Rest of World within the covariate of region. CI = confidence interval; IV = intravenous; SC = subcutaneous

Subgroup analyses for other characteristics

Gender, age, race and region: The CS states (p101) that subgroup analyses of gender, age, race and geographic region all showed that, regardless of these characteristics, subjects treated with mepolizumab achieved a greater reduction in the rate of clinically significant exacerbations than those treated with SoC alone.

FEV_1: The CS states (p107) that a subgroup analysis of MENSA showed that, regardless of baseline percent predicted FEV_1, subjects receiving mepolizumab 75mg IV and 100mg SC achieved a greater reduction in the frequency of exacerbations than those treated with placebo: subjects with >60% percent predicted FEV_1 reported 42% and 43% reduction respectively; subjects with >60%-80% percent predicted FEV_1 reported 63% and 69% reduction respectively; and subjects >80% percent predicted FEV_1 reported 30% and 59% reduction respectively.

Baseline Maintenance Oral Corticosteroid Therapy: The CS states (p108) that a subgroup analysis was undertaken for the MENSA ITT population which assessed the rate of clinically significant exacerbations by baseline oral corticosteroid therapy. In MENSA, most of the subjects were not on mOCS (432/576 [75%]). The RRs for exacerbations for mepolizumab vs. placebo (in the 100 mg SC and 75 mg IV groups) were 0.34 and 0.53 for patients not on mOCS, versus 0.80 and 0.52 for patients on mOCS (Table 27).

Table 27: Rate of clinically significant exacerbations by baseline mOCS therapy (ITT population, MENSA) (CS Table 46)

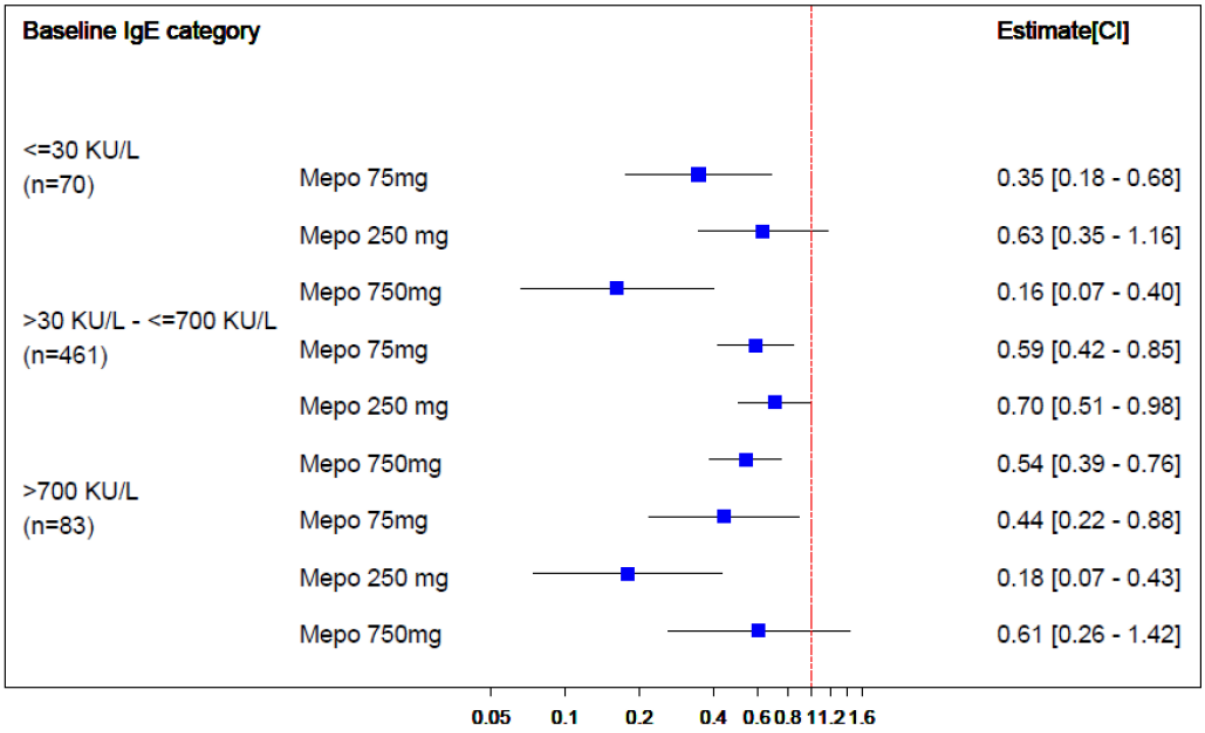
Baseline mOCS therapy	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
No			
N Exacerbation rate/year	147 1.60	143 0.85	142 0.55
Comparison vs. placebo			
RR (mepolizumab/placebo) 95% CI		0.53 0.37, 0.76	0.34 0.23, 0.51
Yes			
N Exacerbation rate/year	44 2.16	48 1.12	52 1.73
Comparison vs. placebo			
RR (mepolizumab/placebo) 95% CI		0.52 0.31, 0.86	0.80 0.49, 1.29

CI = confidence interval; IV = intravenous; mOCS = maintenance oral corticosteroids; SC = subcutaneous

Baseline IgE Concentration in DREAM and MENSA: A subgroup analysis was carried out in both DREAM and MENSA which examined the rate of clinically significant exacerbations by baseline

concentration of IgE. Data from the DREAM subgroup analysis are presented in Figure 7. There was an interaction between total IgE concentration at baseline and treatment group (p=0.021). Multivariate modelling of response showed no differential effect of mepolizumab according to baseline total IgE concentration.

Figure 7: Rate of clinically significant exacerbations by baseline IgE concentration: ratio to placebo (DREAM, CS Figure 15)



CI = confidence interval

In MENSA, most of the subjects had elevated levels of IgE >100µ/mL. Irrespective of baseline IgE concentration, subjects receiving mepolizumab experienced a greater reduction in exacerbation frequency compared with placebo except for subjects in the mepolizumab 100mg SC group with ≤30 U/mL, although the number of patients included in this subgroup was small (Table 28).

Table 28: Analysis of rate of clinically significant exacerbations by baseline IgE concentration (ITT population, MENSA, CS Table 47)

Baseline IgE concentration group	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
≤30 U/mL			
N Exacerbation rate/year	28 0.31	23 0.22	24 0.31
Comparison vs. placebo			
RR (mepolizumab/placebo) 95% CI		0.73 0.34, 1.54	1.00 0.47, 2.10
>30 - ≤700 U/mL			
N Exacerbation rate/year	129 1.66	122 0.78	130 0.68
Comparison vs. placebo			
RR (mepolizumab/placebo) 95% CI		0.47 0.33, 0.69	0.41 0.28, 0.60
>700 U/mL			
N Exacerbation rate/year	25 1.59	34 1.26	28 0.55
Comparison vs. placebo			
RR (mepolizumab/placebo) 95% CI		0.79 0.37, 1.69	0.35 0.13, 0.90

Note: 34 subjects are not shown in this analysis due to not having IgE measured at baseline. CI = confidence interval; IgE = immunoglobulin E; IV = intravenous; SC = subcutaneous

Prior use of omalizumab in MENSA: Most of the subjects did not have prior treatment experience with omalizumab. Treatment with omalizumab was not allowed during the MENSA study. The number of subjects that reported prior use of omalizumab was 21 (11%), 29 (15%) and 25 (13%), in the placebo, mepolizumab 75mg IV and mepolizumab 100mg SC treatments arms, respectively. There appeared to be no marked difference between the prior omalizumab and non-prior omalizumab users in the reduction of clinically significant exacerbations. However, due to the small numbers of prior omalizumab users, it is difficult to draw meaningful conclusions (Table 29).

Table 29: **Analysis of rate of clinically significant exacerbations by previous omalizumab use (ITT population, MENSA, CS Table 48)**

Previous Omalizumab use	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
Yes			
N Exacerbation rate/year	21 2.36	29 0.65	25 1.40
Comparison vs. placebo			
RR (mepolizumab/placebo) 95% CI		0.27 0.12, 0.65	0.59 0.28, 1.26
No			
N Exacerbation rate/year	170 1.62	162 0.99	169 0.74
Comparison vs. placebo			
RR (mepolizumab/placebo) 95% CI		0.61 0.45, 0.84	0.46 0.33, 0.63

CI = confidence interval; IV = intravenous; SC = subcutaneous

4.2.4 Open-label extension studies

4.2.4.1 Description of open-label extension studies

The CS provided data on two open-label, non-randomised, non-controlled extension studies enrolling patients completing the pivotal RCTs (Table 30, CS p154). All patients in these studies received mepolizumab 100mg SC:

- COSMOS, which enrolled patients from MENSA and SIRIUS (completed). Patients either continued mepolizumab without interruption or switched from placebo to mepolizumab. The study duration was 52 weeks (in addition to the initial RCT duration).
- COLUMBA, which enrolled patients from DREAM (ongoing; interim analysis results used with data cut-off in February 2014). Patients had a ≥12 month treatment break before starting or re-starting mepolizumab. The treatment duration with mepolizumab will be up to 3.5 years.

The CS also provides details of an additional non-randomised study, which the CS states was considered less relevant and was not discussed further:

- PK/PD study (MEA114092[40]) evaluating the PK/PD relationship for different doses and formulations of mepolizumab (75mg IV; 12.5mg, 125mg and 250mg SC) in severe asthma patients on high dose ICS with blood eosinophils >300/μL at screening.

Table 30: Open-label extension studies COSMOS and COLUMBA (adapted from CS Tables 74 and 75)

Trial	Intervention	Population	Outcomes	Duration
COSMOS (MEA115661)	• SC Mepolizumab 100mg • Patients previously on mepolizumab continued without interruption; patients previously on placebo started on mepolizumab	• Patients completing MENSA or SIRIUS • Receiving controller medication	Long-term safety and efficacy data	52 weeks (in addition to MENSA or SIRIUS RCT duration of 32 or 24 weeks)
COLUMBA (MEA115666)	• SC Mepolizumab 100mg • Cessation and re-start of mepolizumab with ≥12 month treatment break • Treatment for up to 3.5 years	• Patients having received ≥2 doses study drug in DREAM • Receiving controller medication	Long-term safety and efficacy data	Up to 3.5 years (following ≥12 month treatment break after 52 week DREAM trial)

SC = subcutaneous

A total of 998 patients have been enrolled in COSMOS (N=651) and COLUMBA (N=347; Table 31). More than half of the patients who participated in DREAM (347/616, 56%) enrolled in COLUMBA, with a ≥12 month treatment break between the two studies. Most patients from MENSA (522/576, 91%) and SIRIUS (126/135, 93%) elected to continue treatment and directly rolled over into COSMOS. All patients received mepolizumab 100mg SC in the open-label extension regardless of their treatment assignment in the double-blind parent study. COLUMBA started before COSMOS, thus patients have longer treatment exposure in this study. As of the February 28th, 2014 data cut-off date for the interim analysis, 96% of patients were continuing treatment and there were 643 patient years of exposure. The most common reasons for premature withdrawal from the open-label studies were AEs and withdrawal of consent (1% for each). The As Treated (AT) population consisted of all subjects who received at least one dose of mepolizumab; this represents the primary population for all summaries of efficacy and safety measures.

The demographics for patients in COSMOS and COLUMBA were similar to those of the RCTs from which patients enrolled (Table 32).

Table 31: Patient numbers in open-label extension studies COSMOS and COLUMBA (CS p153-4)

	Receiving mepolizumab 100mg SC	
Trial	**COLUMBA (interim)**	**COSMOS (final)**
% enrolling from RCTs	From DREAM: 347/616 (56%)	From MENSA: 522/576 (91%) From SIRIUS: 126/135 (93%)
Previous treatment		Previous mepolizumab: 414 Previous placebo: 237
N enrolled	**347**	**651**
Withdrawn	22 (6%)	66 (10%)
Continuing treatment (interim)	325 (94%)	N/A
Completed	N/A	585 (90%)
Primary reason for withdrawal, N (%):		
Adverse event	11(2)	
Withdrew consent	14 (2)	8 (2)
Lack of efficacy	19 (3)	8 (2)
Protocol deviation	8 (1)	0
Physician decision	9 (1)	2 (<1)
Lost to follow-up	3 (<1)	1 (<1)
Met protocol stopping criteria	2 (<1)	2 (<1) 1 (<1)

SC = subcutaneous

Table 32: Demographics for COSMOS and COLUMBA, ITT populations (CS p152-3)

Demographic	**COLUMBA (N=347)**	**COSMOS (N=651)**
Age, yr Mean (SD)	52.2 (10.7)	51.1 (13.9)
Gender, (%) Female	65	55
Race, (%) White	92	81
Body Mass Index, kg/m^2 Mean (SD)	28.62 (6.10)	28.02 (5.85)

SD = standard deviation

4.2.4.2 Clinical effectiveness results of open-label extension studies COSMOS and COLUMBA

Rate of exacerbations

The rate of exacerbations per year in COLUMBA was 0.67 (Table 33), which is lower than the rate of 1.24 in the mepolizumab group for the DREAM ITT population (Table 14). The rate of exacerbations per year in COSMOS was 0.93 (Table 33), which is similar to the rate of 0.88 in the mepolizumab group for the MENSA ITT population but slightly higher than the rate of 0.68 for the SIRIUS ITT population (Table 14). The number of patients experiencing ≥1 exacerbation was 151/347 (44%) in COLUMBA and 311/651 (48%) in COSMOS.

In COSMOS, the rates of exacerbations per year remained consistent from the interim report (0.96) to the final report (0.93). The rate of exacerbations per year for subjects previously treated with placebo for 32 weeks in MENSA and switched to mepolizumab also decreased over time during the COSMOS study (from 1.94 to 1.04/year). In COLUMBA, there was an interim period after DREAM where patients were not receiving treatment (range 12-28 months, mean 18.1 months). During this time, subjects experienced an annualised average of 1.74 exacerbations. This number was lower than the 3.6 exacerbations in the year prior to DREAM. Following treatment with SC mepolizumab, the annualised rate of exacerbations was reduced to 0.67.

Exacerbations requiring hospitalisation or ED visit occurred in 7% and 9% of subjects in COLUMBA and COSMOS, whilst exacerbations requiring hospitalisation occurred in 5% and 6% (Table 33).

Table 33: Exacerbations (COSMOS and COLUMBA, AT population) (CS Table 80)

	COLUMBA (Interim) Mepolizumab 100 mg SC N=347[1]	**COSMOS (Final) Mepolizumab 100 mg SC N=651**
On-Treatment Exacerbations		
All exacerbations		
Number of subjects, n (%)	151 (44)	311 (48)
Number of events	301	654
Estimated exacerbation rate/year (95% CI)	**0.67** (0.57, 0.79)	**0.93** (0.83, 1.04)
Exacerbations requiring hospitalisation or ED visit		
Number of subjects, n (%)	25 (7)	59 (9)
Number of events	34	95
Exacerbations requiring hospitalisation		
Number of subjects, n (%)	16 (5)	39 (6)
Number of events	16	65
Post-Treatment Exacerbations[2]		
All exacerbations		
Number of subjects, n (%)	5 (1)	49 (8)
Number of events	5	59
Exacerbations requiring hospitalisation or ED visit		
Number of subjects, n (%)	2 (<1)	10 (2)
Number of events	2	10
Exacerbations requiring hospitalisation		
Number of subjects, n (%)	1 (<1)	8 (1)
Number of events	1	8

1. Includes events that occurred from the start of treatment until 28th February 2014 or the date of withdrawal, but no greater than 4 weeks post last dose. 2. Includes events that occurred in withdrawn subjects beyond their date of withdrawal or that occurred over 4 weeks after their last dose. AT = as treated (all subjects who received ≥1 dose of mepolizumab); CI = confidence interval; ED = emergency department; SC = subcutaneous

Durability of response

COSMOS: Within subjects completing MENSA then COSMOS, the rate of exacerbations per year during the 32-week double-blind period of MENSA was lower for subjects treated with mepolizumab than placebo (0.91 versus 1.94/year; Table 34). During open-label treatment of all subjects with mepolizumab in COSMOS, the rates of exacerbations per year remained low in subjects previously treated with mepolizumab (0.92 for Weeks 32 to 52 and 0.92 for Weeks 52 to 84). The rate of exacerbations for subjects previously treated with placebo in MENSA and switched to mepolizumab decreased over time during COSMOS from 1.94 to 1.04 per year (Table 34).

Equivalent data were not presented in the CS for patients taking part in SIRIUS then COSMOS, or in DREAM then COLUMBA.

Table 34: Exacerbation rate by treatment allocated within MENSA (MENSA and COSMOS, AT population) (CS Table 83)

Treatment period	Placebo (N=191)	Mepolizumab 75 IV/100 SC (N=385)
Subjects who completed COSMOS	159	311
Week 0 - Week 32 (Double-blind)		
Number of events	190	174
Exacerbation rate/year	**1.94**	**0.91**
Week 32 - Week 52 (Open-label)		
Number of events	66	110
Exacerbation rate/year	**1.08**	**0.92**
Week 52 - Week 84 (Open-label)		
Number of events	101	174
Exacerbation rate/year	**1.04**	**0.92**
Subjects with at least 52 Weeks data	170	335
Week 0 - Week 32 (Double-blind)		
Number of events	201	205
Exacerbation rate/year	**1.92**	**0.99**
Week 32 - Week 52 (Open-label)		
Number of events	72	132
Exacerbation rate/year	**1.10**	**1.03**
Subjects with at least 32 Weeks data	180	361
Week 0 - Week 32 (Double-blind)		
Number of events	210	221
Exacerbation rate/year	**1.89**	**0.99**

Note: Includes clinically significant exacerbations from MENSA and all exacerbations from COSMOS MEA115661). Note: Exacerbations summarised according to randomised treatment in MENSA. In general, exacerbations displayed in Weeks 0-32 were experienced on randomised treatment in MENSA, exacerbations displayed in Weeks 32-52 to Weeks 52-84 were experienced on mepolizumab treatment in COSMOS. Weeks 32-52 includes 6 exacerbations experienced in MENSA on mepolizumab. AT = as treated (all subjects who received ≥1 dose of mepolizumab); SC = subcutaneous

Oral corticosteroid use

COSMOS: Within subjects completing SIRIUS then COSMOS, patients on mepolizumab during the double-blind period of SIRIUS reduced their steroid dose from a median of 10 mg/day to 2.5 mg/day

(CS p159-160). During Weeks 44 to 76, the median dose remained low at 2.5 mg/day. The use of OCS for subjects previously treated with placebo for 24 weeks in SIRIUS and switched to mepolizumab decreased over time during the COSMOS study (from 10.0 to 5.0 mg/day).

Lung function

COSMOS: At the time of the first assessment of lung function (Week 16) and continuing through the conclusion of the study, subjects previously treated with placebo showed increases from baseline in pre-bronchodilator FEV_1. Little change was observed in subjects previously treated with mepolizumab.

COLUMBA: Beginning at first time point measured after treatment initiation (Week 12) and continuing through to Week 48, subjects showed mean increases from baseline in pre-bronchodilator FEV_1 at each assessment. In COLUMBA, the baseline mean percent predicted FEV_1 of 60% was consistent with the mean baseline value in DREAM. Mean improvements in pre-bronchodilator FEV_1 of 91 to 144 mL were observed showing an overall improvement in lung function.

Asthma Control Questionnaire (ACQ-5)

COSMOS: At the time of the first assessment (Week 4) and continuing through to Week 52, subjects previously treated with placebo showed decreases (improvements) from baseline in ACQ-5 scores. In subjects previously treated with mepolizumab, improvements achieved following mepolizumab treatment within previous studies MENSA and SIRIUS were sustained.

COLUMBA: Beginning at the first time point measured after treatment initiation (Week 12) and continuing through Week 60, subjects treated with mepolizumab showed decreases (improvements) from baseline in ACQ-5 scores. The mean changes from baseline in ACQ-5 score were greater than the MCID of 0.5 at Weeks 24, 36, 48 and 60.

Blood eosinophils

COSMOS: The geometric mean eosinophil counts for subjects previously treated with placebo were reduced from 280 cells/µL (at baseline) to 50 to 60 cells/µL at most other time points. As expected, for subjects who previously received mepolizumab, overall values were unchanged. Mepolizumab produced a sustained reduction of blood eosinophils through the duration of treatment. The suppression of blood eosinophils in COSMOS was consistent with that in MENSA and SIRIUS.

COLUMBA: Blood eosinophil measurements during treatment showed a decrease of approximately 80% at all time points, therefore also showing a sustained reduction of blood eosinophils through the duration of treatment to date.

4.2.5 Safety of mepolizumab

The CS provided a review of safety evidence and AEs for mepolizumab. Results were presented for the placebo-controlled trials (DREAM, MENSA and SIRIUS) and the non-randomised, non-controlled, open-label extension studies (COSMOS and COLUMBA). Data collection has been completed for COSMOS but is ongoing for COLUMBA (data cut-off of 23rd September 2015). The CS provided safety data collated across the three RCTs. The ERG requested additional data on AEs of special interest; these were provided by the company for each trial separately (clarification response Question A12) and collated across trials by the ERG.

4.2.5.1 Rates of AEs

AEs with relative risk of 1.5 or greater for mepolizumab vs. placebo in RCTs: AEs for which the risk was at least 1.5 times as great for mepolizumab vs. placebo are shown in Table 35 (ordered by relative risk). Eczema was significantly and five times more frequent in the mepolizumab arms than the placebo arms (2.5% vs. 0.5%, RR=5.34, 95% CI 1.25 to 22.78). Nasal congestion and dyspnoea were more than twice as likely to be experienced by subjects taking mepolizumab compared with those taking placebo. Allergic rhinitis and urinary tract infections were approximately 1.6 times as common in the mepolizumab vs. placebo groups.

Table 35: Adverse events with relative risk of 1.5 or greater for mepolizumab vs. placebo for DREAM, MENSA and SIRIUS (adapted from CS Table 89)

Event	Treatment	N	Number (%) with Event		Adjusted Cumulative Proportion [1]	Relative Risk	(95% CI) [2]
Eczema	Placebo	412	2	0.50%	0.50%		
	All Doses	915	23	2.50%	2.60%	5.34	(1.25, 22.78)
Nasal congestion	Placebo	412	4	1.00%	1.00%		
	All Doses	915	24	2.60%	2.50%	2.62	(0.89, 7.72)
Dyspnoea	Placebo	412	4	1.00%	1.10%		
	All Doses	915	23	2.50%	2.30%	2.2	(0.78, 6.20)
Rhinitis allergic	Placebo	412	7	1.70%	1.70%		
	All Doses	915	27	3.00%	2.80%	1.64	(0.70, 3.85)
Urinary tract infection	Placebo	412	9	2.20%	2.10%		
	All Doses	915	32	3.50%	3.40%	1.63	(0.77, 3.47)

[1] Adjusted using Cochran-Mantel-Haenszel weights [2] Calculated using the Cochran-Mantel-Haenszel method. CI = confidence interval

AEs with a frequency of 5% or greater for mepolizumab in RCTs: AEs with a frequency of ≥5% for mepolizumab are shown in Table 36 (ordered by relative risk). Nasopharyngitis and headache had a frequency of more than 20% in the mepolizumab group, which was similar to the placebo groups. All AEs in this category had fairly similar frequencies in the mepolizumab and placebo groups, all with relative risks of less than 1.3.

Rates of AEs in open-label extension studies: In the open-label extension studies, COSMOS and COLUMBA (CS p165), the frequencies of most AEs were slightly higher but generally similar to the reported rates in the placebo-controlled studies. These included nasopharyngitis (30% and 26% for COSMOS and COLUMBA, respectively), upper respiratory tract infection (16% and 13%), headache (14% and 21%) and other infections (COSMOS: bronchitis 12% and sinusitis 10%). The reported frequency for all other AEs for COSMOS was 7% or less.

Table 36: Adverse events with a frequency of 5% or greater for mepolizumab for DREAM, MENSA and SIRIUS (adapted from CS Table 89)

Event	Treatment	N	Number (%) with Event		Adjusted Cumulative Proportion [1]	Relative Risk	(95% CI) [2]
Back pain	Placebo	412	20	4.90%	5.00%		
	All Doses	915	60	6.60%	6.30%	1.26	(0.77, 2.06)
Headache	Placebo	412	74	18.00%	17.80%		
	All Doses	915	195	21.30%	21.30%	1.2	(0.94,1.53)
Nasopharyngitis	Placebo	412	80	19.40%	19.40%		
	All Doses	915	184	20.10%	19.80%	1.02	(0.80,1.30)
Arthralgia	Placebo	412	23	5.60%	5.60%		
	All Doses	915	50	5.50%	5.60%	0.99	(0.61,1.61)
Upper respiratory tract infection	Placebo	412	47	11.40%	11.50%		
	All Doses	915	96	10.50%	10.30%	0.9	(0.64, 1.25)
Bronchitis	Placebo	412	39	9.50%	9.50%		
	All Doses	915	73	8.00%	7.90%	0.83	(0.57, 1.21)
Sinusitis	Placebo	412	40	9.70%	9.80%		
	All Doses	915	68	7.40%	7.60%	0.78	(0.54, 1.13)
Asthma worsening or exacerbation	Placebo	412	61	14.80%	14.90%		
	All Doses	915	89	9.70%	9.10%	0.61	(0.45, 0.84)

[1] Adjusted using Cochran-Mantel-Haenszel weights [2] Calculated using the Cochran-Mantel-Haenszel method. CI = confidence interval

4.2.5.2 AEs of special interest

AEs of special interest were listed in the CS (p166) as: systemic (non-allergic and allergic/hypersensitivity) and local site reactions, cardiac events, infections, and malignancies. Data are shown in Table 37 for the placebo-controlled trials; these were collated by the ERG based on data for each trial provided in the clarification response (Question A12).

Systemic, infusion-related and hypersensitivity reactions: Data on these events were provided in the CS and clarification response but terminology was not always consistent across trials. Infusion-related reactions had an incidence of 4.4% for mepolizumab (all doses) vs. 2.7% for placebo. Rates for IV mepolizumab were 2.3% for 75mg IV, 7.9% for 250mg IV and 12.2% for 750mg IV, whilst there were no cases for mepolizumab100mg SC (CS p164-7 and Table 37).

Rates of "hypersensitivity" reactions in DREAM were 0.7% for mepolizumab all doses vs. 2% for placebo and in MENSA were 2% for mepolizumab vs. 2% for placebo; no comparable data were reported for SIRIUS (clarification response A12). In the open-label extension studies, rates of systemic reactions were 2% and rates of hypersensitivity/allergic reactions were <1% in both COLUMBA and COSMOS. There were no reports of anaphylaxis.

Injection site reactions: The incidence of injection site reactions was 3% for mepolizumab (all doses) and 3% for placebo (CS p166). However, the incidence was higher for mepolizumab administered subcutaneously (8%) than intravenously (1.7%) (Table 37, clarification response A12). The CS reports that injection site reactions were all non-serious, mild to moderate in intensity and the majority resolved within a few days, but that two patients withdrew due to injection site reactions. In the open-label extension studies, rates of injection site reactions for mepolizumab 100mg SC were 9% for COLUMBA and 4% for COSMOS.

Infections: The incidence of all infections (including serious and opportunistic) was similar across the mepolizumab (57%) and placebo groups (58%) in the placebo-controlled trials (Table 37). The incidence of serious infections was also similar (mepolizumab 2.5% vs. placebo 3.4%). In the open-label extension studies, infections occurred in 62% (COLUMBA) and 70% (COSMOS) and serious infections in 1% (COLUMBA) and 4% (COSMOS).

Malignancies: Rates of neoplasms were similar across groups (mepolizumab 0.8% vs. placebo 1.7%), as were rates of malignancies (mepolizumab 0.2% vs. placebo 0.7%, Table 37). In the open-label extension studies, neoplasms occurred in 1% for COLUMBA and 2% for COSMOS.

Cardiac events: Across trials, rates of all cardiac events were similar for mepolizumab (2.9%) and placebo (2.8%), as were rates of serious ischaemic events (0.5% in both groups) (Table 37). However, rates of serious cardiac events were higher for mepolizumab than placebo (0.9% vs. 0.2%), as were rates of serious cardiac, vascular and thromboembolic (CVT) events (1.2% vs.0.7%), though event rates were low. In the open-label extension studies, cardiac events occurred in 4% for COLUMBA and 2% for COSMOS.

Table 37: Adverse events of special interest for DREAM, MENSA and SIRIUS (adapted from CS p164-7 and clarification response A12)

Event	Treatment	N	Number (%) with Event		Relative Risk[1]	(95% CI)
Infusion-related						
Infusion-related reaction	Placebo	412	11	2.7%		
	All doses	915	40	4.4%	1.64	Not reported
	75mg IV	344	8	2.3%	0.87	Not reported
	250mg IV	152	12	7.9%	2.96	Not reported
	750mg IV	156	19	12.2%	4.56	Not reported
	100mg SC	263	0	0%	0	Not reported
Injection site reaction	Placebo	412	14	3.4%		
	All doses	915	32	3.5%	1.03	Not reported
	All doses IV	652	11	1.7%	0.50	Not reported
	100mg SC	263	21	8.0%	2.35	Not reported
Infections						
All infections	Placebo	412	239	58.0%		
	All doses	915	519	56.7%	0.98	Not reported
Serious infections	Placebo	412	14	3.4%		
	All doses	915	23	2.5%	0.74	Not reported
Opportunistic infections	Placebo	257	1	0.4%		
	All doses	454	4	0.9%	2.26	Not reported
Neoplasms						
Neoplasms	Placebo	346	6	1.7%		
	All doses	846	7	0.8%	0.48	Not reported
Malignancies	Placebo	412	3	0.7%		
	All doses	915	2	0.2%	0.30	Not reported
Cardiac events						
Cardiac events/disorders	Placebo	412	12	2.9%		
	All doses	915	26	2.8%	0.98	Not reported
Serious cardiac events	Placebo	412	1	0.2%		
	All doses	915	8	0.9%	3.60	Not reported
Serious CVT events	Placebo	257	3	0.7%		
	All doses	454	11	1.2%	1.65	Not reported
Serious ischaemic events	Placebo	257	2	0.5%		
	All doses	454	5	0.5%	1.13	Not reported

1. Calculated by ERG using percentage rates rather than adjusted cumulative proportions. CI = confidence interval; CVT = cardiac, vascular and thromboembolic; IV = intravenous; SC = subcutaneous

4.2.5.3 Serious adverse events (SAEs) and drug-related AEs

SAEs: Rates of SAEs across the three placebo-controlled trials were 6% for mepolizumab 100mg SC, 10% for mepolizumab 75mg IV and 15% for placebo (CS p169-70). Rates of SAEs per trial were: for DREAM, 14% for mepolizumab all doses vs. 16% for placebo; for MENSA, 8% for mepolizumab all doses vs. 14% for placebo; and for SIRIUS, 1% for mepolizumab 100mg SC vs. 18% for placebo (clarification response Question A12). Similar findings were reported for the extension studies.

SAEs with higher incidence for mepolizumab than placebo were as follows: for mepolizumab, there were two cases (0.2%) of herpes zoster, two cases of hypertension, and two cases of myocardial ischaemia, versus none of any of the above with placebo. The only SAE occurring in more than 1% of

subjects in any arm was the worsening or exacerbation of asthma: 9% for placebo, 2% for mepolizumab 100mg SC, and 6% for mepolizumab 75mg IV.

Investigator-assessed drug-related AEs: The incidence of drug-related AEs, as assessed by a trial investigator, in DREAM, MENSA and SIRIUS was 23% in the mepolizumab 100 mg SC group, 18% in the mepolizumab 75 mg IV group and 16% in the placebo group (Table 38). Infusion-related reactions (potentially drug-related) occurred in 2% for mepolizumab 75mg IV, none for mepolizumab 100mg SC, and 3% for placebo. Injection site reactions occurred in 2% for mepolizumab 75mg IV, 6% for mepolizumab 100mg SC, and 3% for placebo. Headache occurred in 4% for mepolizumab (all doses) vs. 2% for placebo. All other drug-related AEs occurred in less than 2% of subjects.

The reported incidence of drug-related AEs was similar in COSMOS (18%) for mepolizumab 100 mg SC, and injection site reaction (4%) and headache (3%) were again the most frequently reported drug-related AEs. Arthralgia was also reported in 2% of subjects. All other AEs occurred in ≤1% of subjects. Data were not reported for COLUMBA.

Table 38: Drug-related AEs occurring in 3% or more subjects in any group in DREAM, MENSA and SIRIUS (adapted from CS Table 91)

	Number (%) of Subjects					
		Mepolizumab				
Drug-Related Adverse Event	**Placebo N=412**	**100 SC N=263**	**75 IV N=344**	**250 IV N=152**	**750 IV N=156**	**All Doses N=915**
Any Drug-related AE	67 (16)	60 (23)	61 (18)	29 (19)	33 (21)	183 (20)
Infusion-related reaction	11 (3)	0	8 (2)	12 (8)	19 (12)	39 (4)
Headache	10 (2)	13 (5)	11 (3)	6 (4)	5 (3)	35 (4)
Injection site reaction	12 (3)	17 (6)	8 (2)	0	0	25 (3)

AE = adverse event; IV = intravenous; SC = subcutaneous

4.2.5.4 AEs leading to withdrawal from treatment

The rates of AEs leading to the withdrawal of subjects from studies, i.e. the permanent discontinuation of the investigational product, were similar across placebo and mepolizumab groups both in the placebo-controlled trials and the open-label extension studies (between 2% and 5%; Table 39). The only exception was the reported rate for the mepolizumab arms in the MENSA trial (0.3%), which was lower than the placebo arm in MENSA and the placebo and mepolizumab arms in the other trials (0.3%). The reason for this is unclear.

Table 39: Summary of the rates of adverse events leading to permanent withdrawal from all relevant studies

Study	Placebo n/N (%)	Mepolizumab (all doses) n/N (%)
DREAM	6/155 (4%)	22/461 (5%)
MENSA	4/191 (2%)	1/385 (0.3%)
SIRIUS	3/66 (5%)	3/69 (4%)
COSMOS		11/651 (2%)
COLUMBA (interim data cut)		8/347 (2%)

4.2.5.5 Immunogenicity

It was noted in the CS (p171) that patients might develop antibodies to mepolizumab following treatment. In the placebo-controlled trials DREAM, MENSA and SIRIUS, 15/260 (6%) treated with at least one dose of mepolizumab 100 mg SC developed anti-mepolizumab antibodies. It was reported that the anti-mepolizumab antibodies did not discernibly impact upon the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level. Neutralising antibodies were detected in one subject; the implications of this are not discussed further in the CS.

In COSMOS and COLUMBA, 31/646 (5%) and 18/347 (5%) of subjects had confirmed positive anti-mepolizumab antibody results for at least one visit after baseline, at the data cut-offs of 13th May 2015 and 28th February 2014, respectively.

4.2.5.6 Deaths and long-term safety

The CS reported details of nine deaths that occurred across the placebo-controlled trials (n=5) and open-label extension studies (n=4). Three deaths were linked to patients' underlying asthma: 2/5 in the placebo-controlled trials and 1/4 in the open-label extension studies. Two of the four deaths in the open-label extension studies were due to cardiac events. None of the deaths was attributed in the CS to the study drug.

The CS also reported post-treatment AEs, defined as AEs with a start date greater than 4 weeks after the last dose of study medication. Only 4% of subjects from MENSA and SIRIUS, who did not enrol in the open-label extension studies and who had follow-up visits, reported a post-treatment AE. In DREAM, post-treatment AEs were between 20% and 30%. For COSMOS, post-treatment AEs were reported for 107 subjects (16%). The CS also reported that most AEs tended to decrease as time on treatment increased and that there was no pattern of occurrence that would suggest a difference in the AE profile with longer exposure to study medication.

The ERG notes that the longest follow-up for which data are provided for mepolizumab 100mg SC is 84 weeks (in MENSA then COSMOS) although eventually data for up to 3.5 years will be available from COLUMBA. Given that treatment might be expected to be life-long, there is therefore uncertainty regarding the long-term safety of mepolizumab.

4.2.5.7 Summary of safety data

Mepolizumab appears to be generally well-tolerated in severe eosinophilic asthma patients, with the exception of possible increased risks of eczema, nasal congestion, dyspnoea and injection site reactions with mepolizumab. Hypersensitivity reactions, infections and malignancy occurred at similar rates with mepolizumab and placebo. Cardiac events occurred at similar rates with mepolizumab and placebo, whilst rates of serious cardiac events and serious CVT events were slightly higher for mepolizumab (though event rates were low). In terms of SAEs, there were two cases each of herpes zoster, hypertension and myocardial ischaemia for mepolizumab, versus none for placebo.

In both the placebo-controlled trials and open-label studies, 5%-6% of patients treated with mepolizumab 100mg SC developed anti-mepolizumab antibodies, although the implications of this are unclear. There is also no evidence for the long-term safety of mepolizumab 100mg SC beyond 84 weeks (in MENSA then COSMOS) although eventually data for up to 3.5 years will be available from COLUMBA.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Omalizumab is a relevant comparator for patients who exhibit both allergic (IgE) and eosinophilic phenotypes of severe asthma and who would be potentially eligible for either medication. As there are no head-to-head trials comparing mepolizumab and omalizumab, the company undertook a network meta-analysis (NMA) to compare the two treatments indirectly by synthesising trials comparing either drug to a common comparator, standard of care (CS Section 4.10 p127-149).

Search strategy for NMA

The CS reports a literature search for studies of both mepolizumab and omalizumab (described in Section 4.1). The ERG considers the search strategy to be appropriate and would expect it to identify relevant studies of mepolizumab and omalizumab.

Study selection criteria for NMA

The inclusion and exclusion criteria for the NMA are not very clearly laid out in the CS and so are summarised below by the ERG.

Population: The relevant population for the NMA was first defined as severe asthma patients, aged ≥12 years of age, receiving ICS ≥1,000µg/day plus ≥ 1 additional controller, with a documented history of exacerbations. Mepolizumab trials were eligible for inclusion in the NMA if they included people with severe eosinophilic asthma (blood eosinophils ≥150/µL at initiation of treatment or ≥300/µL in prior 12 months). Omalizumab trials were eligible if they included people with allergic asthma (IgE-mediated, positive for allergens, weight 20-150 kg).

The CS states (p128) that the most relevant population would be patients eligible for both mepolizumab and omalizumab. The company was able to identify a subset of patients within the mepolizumab trials who were also eligible for omalizumab. However, the company was not able to identify patients from the omalizumab trials who a) were eligible for mepolizumab or b) met the restrictions in the NICE omalizumab MTA[11] of requirement for continuous or frequent treatment with OCS. Therefore, the company provide NMA analyses and results for three alternative "populations" of patients. The three populations for the NMA are shown in Table 40 (adapted from CS p129).

All three populations included all patients from the omalizumab trials (whether or not they were mepolizumab-eligible, since the company did not have access to subgroup data). In terms of the mepolizumab data, Population 1 ('overlap') and Population 2 ('extended overlap') were restricted to the subset of mepolizumab trial patients who were also eligible for omalizumab, whilst Population 3 ('full trial') included all patients from the mepolizumab trials (whether or not they were omalizumab-eligible).

The available trials also differed in terms of exacerbation history. Since the eligible mepolizumab trials included patients with ≥2 systemic corticosteroid-treated exacerbations in the previous 12 months, the inclusion of omalizumab trials was also restricted by exacerbation history. Population 1 included omalizumab trials with ≥2 systemic corticosteroid-treated exacerbations or ≥1 hospitalisation or ED exacerbation in the previous 12 months, whilst Populations 2 and 3 included omalizumab trials with ≥1 systemic corticosteroid-treated exacerbation in the previous 12 months (to permit inclusion of a wider pool of omalizumab trials).

Table 40: Three alternative populations for NMA (adapted from CS p129)

Population	Mepolizumab trial patients		Omalizumab trial patients	
	Drug eligibility	**Exacerbation history**	**Drug eligibility**	**Exacerbation history**
Population 1 'overlap'	Subgroup eligible for both mepolizumab and omalizumab	≥2 systemic corticosteroid-treated exacerbations in previous 12 months	All patients (omalizumab-eligible but not all mepolizumab-eligible)	≥2 systemic corticosteroid-treated exacerbations or ≥1 hospitalisation/ED exacerbation in previous 12 months
Population 2 'extended overlap'	Subgroup eligible for both mepolizumab and omalizumab	≥2 systemic corticosteroid-treated exacerbations in previous 12 months	All patients (omalizumab-eligible but not all mepolizumab-eligible)	≥1 systemic corticosteroid-treated exacerbation in previous 12 months
Population 3 'full trial' (used for main analysis)	All patients (mepolizumab-eligible but not all omalizumab-eligible)	≥2 systemic corticosteroid-treated exacerbations in previous 12 months	All patients (omalizumab-eligible but not all mepolizumab-eligible)	≥1 systemic corticosteroid-treated exacerbation in previous 12 months

ED = emergency department

The main NMA results in the CS are presented for Population 3 (all omalizumab trial patients with ≥1 systemic corticosteroid-treated exacerbation in past 12 months, and all mepolizumab trial patients with ≥2 systemic corticosteroid-treated exacerbation in past 12 months). The CS states that this is a *"more balanced comparison … than estimates which include subsets of the mepolizumab data but population-level omalizumab data"* (CS p129). However, in the absence of available data for the "true overlap" population (patients who would be eligible for both drugs), and because the "true overlap" population is relatively small (estimated in the CS to be [redacted]% of all mepolizumab-eligible patients), the analysis of Population 3 (all patients from eligible mepolizumab and omalizumab trials) cannot tell us with any certainty how well either drug works in the "true overlap" population.

Scenarios: In addition to the three alternative "populations" of trial patients, the NMA was conducted for four different scenarios in terms of study inclusion (Table 41). Scenarios 1 and 2 were restricted to double-blind RCTs, whereas Scenarios 3 and 4 also included open-label RCTs. Scenarios 1 and 3 included mepolizumab both 100mg SC and 75mg IV arms, whereas Scenarios 2 and 4 were restricted to mepolizumab 100mg SC arms. The main analysis in the CS is presented for Scenario 1 (double-blind RCTs, mepolizumab 100mg SC + 75mg IV) which the ERG considers to be an appropriate choice. Summary results for other scenarios are also presented.

Table 41: Four alternative scenarios for NMA (adapted from CS Table 59)

Scenario	Description
Scenario 1 (used for main analysis)	Double-blind RCTs Mepo 100mg SC + 75mg IV
Scenario 2	Double-blind RCTs Mepo 100mg SC only
Scenario 3	Double-blind + open-label RCTs Mepo 100mg SC only
Scenario 4	Double-blind + open-label RCTs Mepo 100mg SC + 75mg IV

IV = intravenous; RCT = randomised controlled trial; SC = subcutaneous

Interventions: The following interventions were eligible:

- Mepolizumab 100mg SC or 75mg IV. In the main analyses these were pooled for trials that included both doses. A sensitivity analysis assessed the 100mg SC dose (licensed dose) only.
- Omalizumab: maximum of 600mg SC every 2 weeks as in SmPC.

Comparators: The following comparators were eligible:

- Placebo plus standard of care
- Standard of care alone.

Outcomes: The CS states (CS p131) that *"prior to feasibility assessment, a range of pre-specified primary (exacerbation related) and secondary (HRQoL, lung function, asthma control and safety) endpoints were considered based on those included in the mepolizumab clinical trial programme."* The CS then states that *"the final feasible efficacy endpoints based on availability and consistency of the information reported"* were:

- Clinically significant exacerbations (defined as requiring systemic corticosteroids and/or hospitalisation and/or ED visit, as in MENSA and DREAM)
- Exacerbations requiring hospital admissions
- Change from baseline in predicted FEV_1.

The above endpoints appear to be clinically relevant. The CS Appendix 8.7 notes that there were no comparable data for the other listed endpoints across studies of mepolizumab and omalizumab.

Study design: The main NMA included double-blind parallel-group RCTs with a duration of ≥12 weeks. A sensitivity analysis also included open-label randomised studies.

Studies included in NMA

Three mepolizumab studies (MENSA, DREAM and SIRIUS) were identified by the company's systematic review as being potentially relevant. Of these, two (MENSA and DREAM) were included

in the NMA, since SIRIUS did not specify the exacerbation history and did not use a stable OCS dose (CS p132). The ERG considers this to be appropriate (though it is not well explained in the CS).

In total, 19 omalizumab studies were identified by the company's systematic review as being potentially relevant (CS p128). Of these, five were stated in the CS (p131) to *be "eligible for endpoint analysis"*, whilst four *"reported relevant outcome data."* The difference between these definitions is not clear. The CS provides reasons for exclusion of the remaining studies (p132-133).

The final NMA included two double-blind RCTs of omalizumab: INNOVATE (Humbert *et al*., 2005[37]) and EXTRA (Hanania *et al*., 2011[38]). A third double-blind RCT (Chanez *et al*., 2010[41]) was potentially eligible but relevant outcome data were not available. In addition, two randomised open-label RCTs were included in sensitivity analyses: Niven *et al*. (2008[42]) and EXALT (Bousquet *et al*., 2011[43]). Inclusion of the above studies is summarised in the CS (p134-136). A summary of studies with data for each scenario and outcome for Population 3 ('full trial') is provided in Table 42 (adapted from CS p134-136). A summary of the number of studies included the NMA for each population, scenario and outcome is provided in Table 44.

Table 42: Studies included in NMA for each scenario and outcome for Population 3 'full trial' (adapted from CS Table 59 and 60)

Scenarios	Outcomes	Eligible mepo RCTs		Eligible oma RCTs	
1. Double-blind RCTs Mepo 100mg SC + 75mg IV **(used for main analysis)**	Exacerbations	2	MENSA DREAM	2	INNOVATE Humbert 2005[37] EXTRA Hanania 2011[38]
	Hospitalisations	2	MENSA DREAM	1	INNOVATE Humbert 2005[37]
	FEV_1	2	MENSA DREAM	1	INNOVATE Humbert 2005[37]
2. Double-blind RCTs Mepo 100mg SC only	Exacerbations	1	MENSA	2	INNOVATE Humbert 2005[37] EXTRA Hanania 2011[38]
	Hospitalisations	1	MENSA	1	INNOVATE Humbert 2005[37]
	FEV_1	1	MENSA	1	INNOVATE Humbert 2005[37]
3. Double-blind + open-label Mepo 100mg SC only	Exacerbations	1	MENSA	4	INNOVATE Humbert 2005[37] EXTRA Hanania 2011[38] Niven 2008[42] EXALT Bousquet 2011[43]
	Hospitalisations	1	MENSA	2	INNOVATE Humbert 2005[37] EXALT Bousquet 2011[43]
	FEV_1	1	MENSA	1	INNOVATE Humbert 2005[37]
4. Double-blind + open-label Mepo 100mg SC + 75mg IV	Exacerbations	2	MENSA DREAM	4	INNOVATE Humbert 2005[37] EXTRA Hanania 2011[38] Niven 2008[42] EXALT Bousquet 2011[43]
	Hospitalisations	2	MENSA DREAM	2	INNOVATE Humbert 2005[37] EXALT Bousquet 2011[43]
	FEV_1	2	MENSA DREAM	1	INNOVATE Humbert 2005[37]

FEV_1 = forced expiratory volume in 1 second; IV = intravenous; mepo = mepolizumab; oma = omalizumab; RCT = randomised controlled trial; SC = subcutaneous

4.4 Critique of the indirect comparison and/or multiple treatment comparison

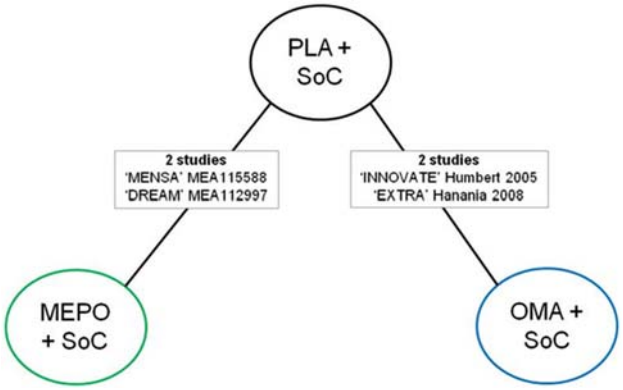
Summary of analyses undertaken

A NMA was performed to compare the treatment effects of mepolizumab, omalizumab and SoC for three outcomes: (i) clinically significant exacerbations; (ii) exacerbations requiring hospitalisation, and; (iii) change from baseline in predicted FEV_1. Separate NMAs were undertaken for each outcome.

Network diagrams for these analyses based on the `full trial' Population 3, and Scenario 1 (double-blind RCTs, mepo 100mg SC + 75mg IV) are shown in Figure 8 (clinically significant exacerbations) and

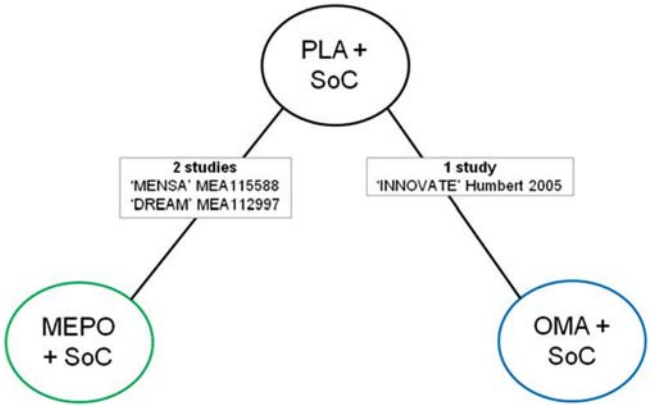
Figure 9 (exacerbations requiring hospitalisation and change from baseline in predicted FEV_1). The results of these analyses were deemed by the company to be most relevant to the decision problem and thus are used for the base case economic evaluation presented in Section 5.2. Sensitivity analyses were also conducted for Population 3 Scenarios 2-4 (CS p138) and for Populations 1 and 2, all scenarios (CS Appendix 8.7). For the sensitivity analyses, only the RRs and mean differences (MDs) of mepolizumab compared with omalizumab were provided. A full summary of all the NMA results and the number of studies included by population and scenario is provided in Table 44 (fixed effect model) and Table 45 (random effects model).

Figure 8: Network diagram for Population 3 'Full trial' (Scenario 1 Mepo 100mg SC+75mg IV, double-blind RCTs) – Clinically significant exacerbations (CS Figure 20)



MEPO = mepolizumab; OMA = omalizumab; PLA = placebo; SoC = standard of care

Figure 9: Network diagram for Population 3 'Full trial' (Scenario 1 Mepo 100mg SC + 75mg IV, double-blind RCTs) – Exacerbations requiring hospitalisation and change from baseline in predicted FEV_1 (CS Figure 22)



FEV_1 = forced expiratory volume in 1 second; MEPO = mepolizumab; OMA = omalizumab; PLA = placebo; SoC = standard of care

Comparability of included trials

Heterogeneity between trials included in the NMA is acknowledged in the CS. In particular, it is noted that *"the distribution of severity (as indicated by exacerbation history) is likely to differ somewhat between the mepolizumab and omalizumab patients included in any approximated `overlap' analysis in this NMA"* (CS p128-129). Exacerbation history is higher in the mepolizumab than omalizumab trials. This variable is identified as a potential treatment effect modifier and so this imbalance may lead to biased estimates of treatment effects which may be expected to favour mepolizumab (since a higher treatment effect would be expected in a more severe asthma population). Despite this, the trials are considered to be *"sufficiently similar to conduct the comparisons"* (CS p148). The use of meta-regression to account for the observed heterogeneity between trials is discussed in the CS but was deemed not to be possible due to the small number of studies. The ERG considers this to be reasonable but notes some ambiguity in that the methods section of the CS (p137) states that *"meta-regression and bias adjustment in the presence of heterogeneity was conducted. A constant interaction effect was assumed for all treatments."*

Fixed and random effects models

The CS performed analyses using both fixed effects and random effects models, with the final model chosen independently for each outcome, population and scenario on the basis of the observed residual deviance and deviance information criterion (DIC). The DIC provides a relative measure of goodness-of-fit that penalises complexity and can be used to compare different models for the same likelihood and data. However, these measures were generally very similar across models, and for the main analyses the CS concludes *"The DICs suggested there was little to choose between the models."* The ERG therefore considers that the company's choice of a fixed effects model over random effects for

the main results has not been properly justified. Moreover, there is inconsistency in the use of fixed or random effects for the sensitivity analyses, with no justification of model choice provided.

For the random effects models it is stated that uninformative prior distributions were used for all calculations, with a Uniform distribution with range 0 to 5 for the between-trial standard deviation (CS p62). For the main analysis of clinically significant exacerbations, based on the `full trial' Population 3 and Scenario 1, this choice of prior has been adhered to, but more restrictive priors were in fact required for at least some other endpoints and scenarios. The reported summaries of the estimated between-study SD indicate that there may not have been enough information with which to update the prior distributions. In this case a weakly informative prior that reflects reasonable prior beliefs should be used. The ERG notes that these stated concerns do not apply to the network used to inform the cost effectiveness model.

The ERG considers that, given the stated concerns over potential heterogeneity between studies, a random effects model would be appropriate for all populations, scenarios and endpoints, with the use of a weakly informative prior considered where appropriate. Results from the fixed effects NMA should be interpreted with caution as they may underestimate the uncertainty surrounding the estimated treatment effects.

Main results of NMA

The input data for Population 3 Scenario 1 (i.e. the individual trial data for the mepolizumab and omalizumab trials) are provided in

Table 43. A full summary of all the NMA results by population and scenario is provided in Table 44 (fixed effect model) and Table 45 (random effects model).

Based on results from the fixed effects NMA in Population 3, the CS concludes that mepolizumab is associated with a reduction in clinically significant exacerbations compared with omalizumab (for Scenario 1, RR=0.664, 95% CrI 0.513, 0.860, Table 44). Conversely, mepolizumab is stated to be broadly comparable to omalizumab for exacerbations requiring hospitalisation (Scenario 1, RR=0.932, 95% CrI 0.350, 2.490) and change from baseline in predicted FEV_1 (Scenario 1, RR=0.645, 95% CrI -2.652, 3.959). Despite making this overall summary based on the presented evidence, the company acknowledges that these results should be treated with caution since the utilised studies include a broader patient population, not all of whom are eligible to receive both treatments under current recommendations. In addition to this, the ERG considers that given the stated concerns in heterogeneity between trials, the assumption of no between-study variance (fixed effects model) should be interpreted with caution. Based on the results from the random effects NMA, the reduction in clinically significant exacerbations for mepolizumab compared with omalizumab is not statistically significant (for Scenario 1, RR=0.664, 95% CrI 0.283, 1.498, Table 45).

The CS states that the results are consistent across the alternative populations and scenarios considered in the sensitivity analyses. For clinically significant exacerbations the direction of treatment effect is consistent across populations (RRs for fixed effects, Scenario 1: 0.761 (95% CrI 0.492, 1.176) for Population 1, 0.752 (95% CrI 0.522, 1.079) for Population 2, 0.664 (0.513, 0.860) for Population 3, Table 44), with the results indicating a stronger treatment effect in favour of mepolizumab as the evidence base is expanded. However, the comparison is only statistically significant for Population 3 and only for the fixed effects model. For exacerbations requiring hospitalisation and change from baseline in predicted FEV_1, the direction of the treatment effect is reversed to favouring omalizumab when a smaller evidence base is considered (Populations 1 and 2, Table 44), although the treatment effects are not statistically significant.

The CS notes two reasons why the NMA results may be biased in favour of mepolizumab. Firstly, the mepolizumab trials included more severe patients (≥2 exacerbations) than the omalizumab trials (≥1 exacerbation) and since a higher treatment effect would be expected in a more severe population this may bias the results in favour of mepolizumab (CS p148). Secondly, a *post hoc* analysis of the EXTRA trial[44] showed that patients with higher eosinophil count at baseline may have a greater reduction in exacerbations with omalizumab compared with the wider patient groups in the included omalizumab trials; again this may bias the results in favour of mepolizumab (CS p149).

The CS concludes that it is a reasonable assumption that in the overlap population mepolizumab would be at least as effective as omalizumab (CS p149).

Table 43: Input data for NMA population 3 `Full trial', scenario 1 (double-blind RCTs Mepo 100mg SC + 75mg IV) (adapted from CS Tables 62, 66 and 70)

Included MEPO data	Rate Ratio MEPO vs. PLA (95% CI)		Mean difference MEPO vs. PLA (95% CI)
	Clinically significant exacerbations	Exacerbations requiring hospitalisation	Change from baseline in % predicted FEV_1
MENSA	0.503 (0.391, 0.647)	0.442 (0.191, 1.022)	3.302 (0.630, 5.433)
DREAM	0.485 (0.353,0.668)	0.589 (0.239,1.451)	4.257 (0.961,7.552)
Included OMA data	**Rate Ratio OMA vs. PLA (95% CI)**		**Mean difference MEPO vs. PLA (95% CI)**
	Clinically significant exacerbations	**Exacerbations requiring hospitalisation**	**Change from baseline in % predicted FEV_1**
INNOVATE	0.738 (0.552,0.998)	0.540 (0.250, 1.166)	2.80 (0.100, 5.500)
EXTRA	0.750 (0.610,0.920)	NA	NA

CI = Confidence interval; FEV_1 = forced expiratory volume in 1 second; MEPO = Mepolizumab; NA = Not applicable; OMA =Omalizumab; PLA = Placebo;

Table 44: Results of fixed effect NMA for all endpoints, populations and scenarios. Rate ratios (RR) and mean differences (MD) of mepolizumab compared to omalizumab

NMA Outcome	Scenario	Population 3 `Full trial'			Population 2 `Extended overlap'			Population 1 `Overlap'		
		N^1	N^2	Mean/Median* (95% CrI)	N^1	N^2	Mean/Median* (95% CrI)	N^1	N^2	Mean/Median* (95% CrI)
Clinically significant exacerbations	1. Double-blind RCTs only; Mepo 75mg IV + 100mg SC	2	2	RR 0.664 (0.513,0.860)	2	2	RR 0.752 (0.522, 1.079)	2	1	RR 0.761 (0.492, 1.176)
	2. Double-blind RCTs only; Mepo 100mg SC	1	2	RR 0.634 (0.449, 0.892)	1	2	RR 0.656 (0.385, 1.114)	1	1	RR 0.664 (0.371, 1.187)
	3. Double-blind + open label; Mepo 100mg SC	1	4	Not reported	1	4	Not reported	1	2	RR 0.846 (0.486, 1.467)
	4. Double-blind + open label; Mepo 75mg IV + 100mg SC	2	4	Not reported	2	4	Not reported	2	2	RR 0.969 (0.655, 1.432)
Exacerbations requiring hospitalisation	1. Double-blind RCTs only; Mepo 75mg IV + 100mg SC	2	1	RR 0.932 (0.350, 2.490)	2	1	*As population #1*	2	1	RR= 1.348 (0.338,5.319)
	2. Double-blind RCTs only; Mepo 100mg SC	1	1	RR 0.576 (0.155, 2.126)	1	1	*As population #1*	1	1	RR 0.194 (0.016, 2.317)
	3. Double-blind + open label; Mepo 100mg SC	1	2	RR 0.686 (0.200,2.341)	1	2	RR 0.230 (0.020, 2.644)	1	1	*As scenario 2*
	4. Double-blind + open label; Mepo 75mg IV + 100mg SC	2	2	RR 1.110 (0.467, 2.646)	2	2	RR 1.605 (0.432,5.882)	2	1	*As scenario 1*
Change from baseline in % predicted FEV_1	1. Double-blind RCTs only; Mepo 75mg IV + 100mg SC	2	1	MD 0.645 (-2.652,3.959)	2	1	*As population #1*	2	1	MD -0.125 (-4.288,4.028)
	2. Double-blind RCTs only; Mepo 100mg SC	1	1	MD 0.243 (-3.606, 4.097)	1	1	*As population #1*	1	1	MD -0.975 (-6.329,4.360)
	3. Double-blind + open label; Mepo 100mg SC	1	1	*As scenario 2*	1	1	*As population #1*	1	1	*As scenario 2*
	4. Double-blind + open label; Mepo 75mg IV + 100mg SC	2	1	*As scenario 1*	2	1	*As population #1*	2	1	*As scenario 1*

* Median is presented for RR, Mean is presented for MD. N^1=number of mepolizumab studies included in analysis; N^2=number of omalizumab studies included in analysis. CrI = credible interval; FEV_1 = forced expiratory volume in 1 second; IV = intravenous; MD = mean difference; RR = rate ratio; SC = subcutaneous

Table 45: Results of random effects NMA for all endpoints, populations and scenarios

NMA Outcome	Scenario	Population 3 `Full trial'			Population 2 `Extended overlap'			Population 1 `Overlap'		
		N^1	N^2	Mean/Median* (95% CrI)	N^1	N^2	Mean/Median* (95% CrI)	N^1	N^2	Mean/Median* (95% CrI)
Clinically significant exacerbations	1. Double-blind RCTs only; Mepo 75mg IV + 100mg SC	2	2	RR 0.664 (0.283,1.498) SD=0.129 (0.005,1.291)	2	2	Not reported	2	1	Not reported
	2. Double-blind RCTs only; Mepo 100mg SC	1	2	RR 0.636 (0.318,1.291) SD=0.139 (0.006,0.475)	1	2	Not reported	1	1	Not reported
	3. Double-blind + open label; Mepo 100mg SC	1	4	RR 0.771 (0.218,2.946)	1	4	RR 0.803 (0.216, 3.167)	1	2	Not reported
	4. Double-blind + open label; Mepo 75mg IV + 100mg SC	2	4	RR 0.798 (0.414,1.613)	2	4	RR 0.913 (0.436, 2.09)	2	2	Not reported
Exacerbations requiring hospitalisation	1. Double-blind RCTs only; Mepo 75mg IV + 100mg SC	2	1	RR=0.937 (0.285,3.059) SD=0.228 (0.011,0.484)	2	1	Not reported	2	1	Not reported
	2. Double-blind RCTs only; Mepo 100mg SC	1	1	RR=0.578 (0.121,.736) SD=0.25 (0.011,0.488)	1	1	Not reported	1	1	Not reported
	3. Double-blind + open label; Mepo 100mg SC	1	2	Not reported	1	2	Not reported	1	1	Not reported
	4. Double-blind + open label; Mepo 75mg IV + 100mg SC	2	2	Not reported	2	2	Not reported	2	1	Not reported
Change from baseline in % predicted FEV_1	1. Double-blind RCTs only; Mepo 75mg IV + 100mg SC	2	1	0.653 (-2.882,4.234) SD=0.488 (0.024,0.974)	2	1	Not reported	2	1	Not reported
	2. Double-blind RCTs only; Mepo 100mg SC	1	1	0.270 (-3.902,4.511) SD=0.5 (0.025,0.974)	1	1	Not reported	1	1	Not reported
	3. Double-blind + open label; Mepo 100mg SC	1	1	*As scenario 2*	1	1	Not reported	1	1	Not reported
	4. Double-blind + open label; Mepo 75mg IV + 100mg SC	2	1	*As scenario 1*	2	1	Not reported	2	1	Not reported

* Median is presented for RR, Mean is presented for MD. N^1=number of mepolizumab studies included in analysis; N^2=number of omalizumab studies included in analysis. CrI = credible interval; FEV_1 = forced expiratory volume in 1 second; IV = intravenous; MD = mean difference; RR = rate ratio; SC = subcutaneous

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness has been undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The clinical effectiveness evidence in the CS is mainly based on three RCTs comparing add-on mepolizumab against placebo plus standard of care in patients with severe eosinophilic asthma, plus two open-label extension studies. The submitted evidence is consistent with the final NICE scope with respect to the interventions, comparators and relevant outcomes assessed.

The population in the final NICE scope is *"adults with severe eosinophilic asthma"* but there are difficulties in specifying the degree of severity and eosinophilia. Patients in the ITT populations had ≥2 exacerbations in the previous year and/or use of mOCS, whilst two of three trials specified a blood eosinophil level of ≥150/μL at screening or ≥300/μL in the previous 12 months. The CS also defined two 'GSK proposed populations' based on exacerbation history, eosinophil count and use of mOCS. The ERG considers that the *post hoc* analyses used to justify the GSK populations should be interpreted with caution, particularly the blood eosinophil cut-off of ≥150 cells/μL at screening. The criterion of ≥4 exacerbations in the previous year appears more clinically robust.

Mepolizumab reduced clinically significant exacerbations to approximately a third to a half of placebo rates across the MENSA and DREAM trials in the ITT and GSK populations (RRs= 0.35 to 0.51 which were statistically significant), and to approximately two-thirds in the SIRIUS trial of mOCS users (RRs= 0.68 to 0.81, statistically significant in the ITT population but not the GSK populations). Exacerbations requiring hospitalisation were reduced to approximately half the placebo rates across the ITT and GSK populations. A range of HRQoL measures showed differences between mepolizumab and placebo which were borderline for clinical and statistical significance across ITT and GSK populations.

In the SIRIUS trial of mOCS users, the primary endpoint of percentage reduction in OCS dose whilst maintaining asthma control favoured mepolizumab over placebo with ORs of 1.8 to 2.8 (statistically significant for the ITT population, but not the GSK population) and absolute differences of 13% to 26% across populations. Secondary outcomes (results are summarised here for the GSK PP) included reduction in OCS dose by at least 50% (OR 1.6, absolute difference 10%); reduction in OCS dose to ≤5 mg (also OR 1.6, absolute difference 10%); and complete cessation of OCS use (OR 1.4, absolute difference 5%); results were not significant in the GSK PP, though numbers of patients included in the sub-populations were small.

Based on the NMA, mepolizumab reduced clinically significant exacerbations versus omalizumab (RR=0.664); this was statistically significant in the fixed effects model but not the random effects model. Mepolizumab was comparable to omalizumab for exacerbations requiring hospitalisation and in FEV_1 impact.

Reported rates of injection site reactions (for SC mepolizumab), infusion-related reactions (for IV mepolizumab), eczema, nasal congestion and dyspnoea were higher with mepolizumab than placebo. There were small increases over placebo in serious cardiac events, hypertension, myocardial ischaemia and herpes zoster. Hypersensitivity reactions, infections, malignancies and "all cardiac events" had similar rates for mepolizumab and placebo. Anti-mepolizumab antibodies developed in 5-6% of subjects and neutralising antibodies in one subject.

5 COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

In the first part of this section the ERG provides a critique of the literature searches for the cost effectiveness review and the parameters used to inform the company's economic models.

5.1.1 The objective of cost effectiveness review

Cost effectiveness and resource use

The CS reports a systematic literature review of published cost-effectiveness studies. An appropriate selection of databases were searched including Medline, EMBASE, the Cochrane Library and specialist economic databases such as NHS EED and EconLit. No date or language limits were applied. The searches are reproduced in full however, as with the clinical effectiveness searches, the numbers of results have been omitted, making it difficult for the ERG to replicate and accurately assess them.

A PRISMA flowchart is provided, however the ERG would have preferred to see results retrieved *per database* rather than *per platform*.

The cost-effectiveness and resource use searches of Medline/EMBASE (via ProQuest) included search terms for resource utilisation and costs, and for HTA; however, some of these terms were searched only in titles and abstracts and not in other fields such as subject headings. In their response to the clarification letter (question A1), the company stated that *"all systematic reviews were conducted by experienced systemic literature reviewers"* and that *"search strings are based on our usual list of search terms/strings for the topics."* As in the clinical effectiveness review, the ERG would have been more reassured by the use of validated filters (with appropriate acknowledgement).

A separate search was conducted of Medline In Process, this time using Ovid (though it is unclear why this platform was chosen when the same source could have been searched on PubMed, with the added option of including publisher–supplied papers ahead of print). The ERG also notes that there appear to be some typographical errors in this search e.g. the use of unnecessary hairpin brackets <> around the first term "Asthma*" and, in line 2, "asthmaxxx", which is not valid syntax for this platform.

Asthma-related mortality

A separate systematic literature review was conducted to find studies reporting asthma-related mortality.

Medline and EMBASE were searched together and while there was some attempt to construct an effective multi-file search by searching for "Asthma" and "Mortality" in both MeSH and Emtree headings, it appears that the latter term was not exploded in MeSH, meaning that articles indexed with narrower headings such as "Cause of death" and "Fatal Outcome" would not be retrieved.

The ERG attempted to replicate this search on the Ovid platform (on 7th January 2016) but retrieved 2,323 results - significantly more results than the 857 reported (across all databases) in the CS. As no date is recorded for the company's search, it was not possible to exclude results added more recently, however, this is unlikely to fully explain such a large disparity

The CS (Section 5.3.6) states that the review sought to identify "UK studies." However, the search strategy used for Medline and Embase via ProQuest (CS appendix 8.12.2, Table 94) includes MeSH headings for a number of countries including the USA, Australia, Japan, Germany and France as well as Great Britain. The equivalent Emtree headings (e.g. "United Kingdom") have not been included nor have any free-text occurrences of country names and abbreviations (e.g. "Britain", "British", "UK") which may have occurred in other fields such as titles or abstracts. However, as the ERG believes that data from jurisdictions other than the UK could provide useful information this does not represent a limitation of the search.

The ERG ran additional searches including these free text terms to assess the impact on the results retrieved by the Medline/EMBASE search, and found an additional 218 studies. The ERG notes that some of these may have been added after the original searches were run, or may have been picked up by the other searches.

The CS also includes a search of Medline In Process via Ovid; this contained some typographical errors (for example, "Asthma. Sh" in line #2 is not valid syntax for Ovid). However, as results for each search string are again omitted, the impact of these errors on the results retrieved is unclear.

Of the 845 results retrieved in total by all the searches, a substantial number of citations (n=728) were excluded at the screening stage. According to the exclusion criteria (CS Appendix 8.12.2, Table 96), review articles were excluded if cost-effectiveness was not their major focus. If this was the intention from the outset, it might have proved more efficient to apply a validated cost-effectiveness filter as part of the search strategy.

HRQoL and utility studies

A further search was conducted for evidence on patient-reported outcomes and utility values in severe and eosinophilic asthma. The search included Medline, Medline In Process (via PubMed), EMBASE, and a selection of HTA and conference proceedings websites.

The reporting of this search is somewhat confusing as it combines update searches with earlier searches conducted for previous reviews undertaken by the company. The prose description of the search process is vague and difficult to follow, making claims which are not supported by the search strategies presented. For example, in the Appendices (Section 18.13.1) the text states that *"The indexed database search strategy was designed to identify studies in humans indexed with titles and abstracts (hereby excluding those indexed as title only)."* However, in the search strategy which follows terms have been searched in titles OR abstracts (as is, in any case, best practice).

Despite these issues, the ERG is broadly confident that the searches undertaken would have identified all relevant HRQoL and utility studies.

AEs

The company conducted a "*targeted search*" for resource use / utility studies on AEs in severe asthma for which OCS maintenance therapy is used. The searches focussed on the condition and 6 of the most common AEs but did not include terms for mepolizumab or its comparators.

5.1.2 The inclusion and exclusion criteria used in the study selection

The systematic literature review conducted by the company to identify cost-effectiveness studies relevant to the decision problem used the inclusion and exclusion criteria listed in

Table 46.

Table 46: Eligibility criteria used in the study selection (reproduced from CS Table 96)

Dimension	Inclusion criteria	Exclusion criteria
Disease and treatment	Severe asthma*	• Other diseases • Asthma of other levels of severity
Patient group	Adults and children (≥12 years of age)**	Children of < 12 years of age
Article type	Original cost-effectiveness analysis of the "mabs" and all maintenance OCS	• Review articles in which cost-effectiveness is not the major focus • Letters or editorials that comment on results of an economic evaluation published elsewhere.
Publication time	Without restriction	NA
Publication language	Without restriction – all languages	No exclusion due to language

*Protocol deviation was decided upon by also including studies with moderate-to-severe asthma; severe asthma alone retrieved fewer results and therefore deemed too limiting.
**The original searches were conducted prior to the regulatory process and therefore the age inclusion reflected the trial inclusion criteria. This was not altered at a later date to reflect the regulatory application. Studies still deemed relevant for informing model structural parameters.

5.1.3 Findings and conclusions of the cost effectiveness review

The systematic literature review undertaken by the company identified 3,726 unique records. Of these records, 3,463 records were excluded based on their title or abstract. Of the remaining 263 records, 17 studies were excluded for the following reasons:

- Not severe asthma: 70
- Not adults or children ≥12: 23
- Not "mabs" / maintenance OCS: 18
- Not original CE or RU / cost analysis study: 66
- Other reasons: 28

Of the remaining 58 studies, 15 were cost-effectiveness studies and deemed eligible for inclusion and 43 were RU / cost studies, which were excluded. The 15 cost-effectiveness studies are outlined in Table 97 of the CS. Two of these studies reported the cost-effectiveness of treatments in moderate-to-severe asthma but were not considered relevant. The remaining 13 studies reported the cost-effectiveness of omalizumab compared with SoC. Two of these studies were deemed relevant to the appraisal by the company, considering the patient population, perspective, and country of study: Norman *et al.*[45] and Faria *et al.*[46]

No conclusion from the cost-effectiveness review was presented by the company; instead, the CS argues that none of the identified studies captured the cost effectiveness of mepolizumab compared

with SoC alone. As such, the company presented the cost-effectiveness results from a *de novo* model developed for this appraisal and described in Section 5.2 of this report.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 NICE reference case

A summary of the key features of the company's *de novo* model is provided in Table 47.

Table 47: Key features of the company's *de novo* model

Population, intervention, comparators and outcomes.	See Table 1
Starting age	50.1 years
Time horizon	Approximately 92 years, assumed representative of lifetime
Cycle length	Four weeks
Half-cycle correction	Not included
Measure of health effects	QALYs
Primary health economic outcome	Incremental cost per QALY gained
Discount of 3.5% per annum for utilities and costs	Costs and benefits were discounted at 3.5% per annum.
Perspective	The NHS in England.

5.2.2 Population

The company has focussed on a subgroup of the adult population with severe refractory eosinophilic asthma where mepolizumab "showed enhanced clinical benefit." This subgroup, which the ERG has termed the GSK PP, is defined as follows:

Adults (≥18 years) with a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year or dependent on mOCS.

The CS also presents the results of the economic analysis for a subset of this population where patients on mOCS with less than 4 exacerbations are excluded, which the ERG has termed the GSK PP excl. stable mOCS.

For the comparison with omalizumab the company did not have access to the individual patient data required to assess the effectiveness of omalizumab in the GSK PP and the GSK PP excl. stable mOCS. The company undertook a simplistic approach assuming that the ITT populations of MENSA

and the omalizumab trials could be compared. Table 48 describes the different populations used in the economic analysis and the comparators used in each case.

Table 48: Different populations used in the economic analysis and the comparators analysed

		Add-on mepolizumab vs.	
BTS/SIGN treatment step	**Population**	**SoC**	**Add-on omalizumab**
4/5	**GSK PP** *Patients who have a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year and/or dependency on maintenance OCS*	✓	-
4/5	**GSK PP excl. stable mOCS** *Patients who have a blood eosinophil count of ≥150 cells/μL at initiation of treatment; and ≥4 exacerbations in the previous year*	✓	-
4/5	**ITT Population** *Patients who have a blood eosinophil count of ≥150 cells/μL at initiation of treatment or ≥300 cells/μL in the prior 12 months; and ≥2 exacerbations in the previous year*	✓	✓

The average start age of the cohort was 50.1 years and 42.9% were males, based on the population of the MENSA trial.

5.2.3 Interventions and comparators

Intervention: Mepolizumab

Mepolizumab (brand name Nucala®) is a humanised anti-IL5 monoclonal antibody indicated for adults as an add-on therapy to treat severe refractory eosinophilic asthma and is administered as a 100mg fixed-dose 4-weekly SC injection. The company assumes that patients would be treated with mepolizumab for a year before a continuation criterion was applied. Those patients who did not experience a worsening of the exacerbation rate during this period compared with the previous year were assumed to remain on treatment. The treatment duration proposed by the company in their base case analysis is 10 years.

Comparator: SoC

SoC represents the primary comparator in this appraisal. According to BTS/SIGN guidelines, patients at Steps 4 and 5 are on high dose ICS and one or more additional maintenance treatments (such as a long-acting beta agonist (LABA), leukotriene receptor antagonist or theophylline). Patients at Step 5 have limited alternative treatment options beyond mOCS.

Comparator: Omalizumab

Omalizumab (brand name Xolair®) is a humanised monoclonal anti-IgE antibody indicated in adults and adolescents (≥12 years) as add-on therapy to improve asthma control in patients with severe persistent allergic asthma. Dose and dosing frequency of omalizumab varies across patients depending on the patient's body weight and IgE level. Omalizumab is available as a pre-filled syringe (PFS) and is administered subcutaneously every 2 or 4 weeks. Omalizumab is recommended by NICE as an option for treating severe persistent confirmed allergic IgE mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year). Patients receive omalizumab treatment for 16 weeks and then treatment is discontinued unless the clinician's assessment of the effectiveness of the treatment is good or excellent. The company estimated that approximately [redacted] of the patients in the GSK PP would also be eligible for omalizumab (in accordance with the omalizumab licence and NICE guidance (TA278)).

5.2.4 Perspective, time horizon and discounting

The perspective of the economic evaluation was that of the NHS in England and a PSS perspective is considered qualitatively in section 5.5.4 of the CS. A lifetime horizon was also appropriately used to capture differential mortality rates between the intervention and the comparators. This was estimated using a time horizon of 4,800 weeks (approximately 92 years). After this time, the proportion of patients alive in the company's base case was negligible (less than 0.00001%) in all treatment arms.

The company used discount rates of 3.5% per annum for both costs and benefits, in line with the NICE Reference Case.[47] Discount rates were calculated for each 4-week cycle. A half-cycle correction was not implemented, however the ERG notes that given the short cycle length, its impact would be negligible.

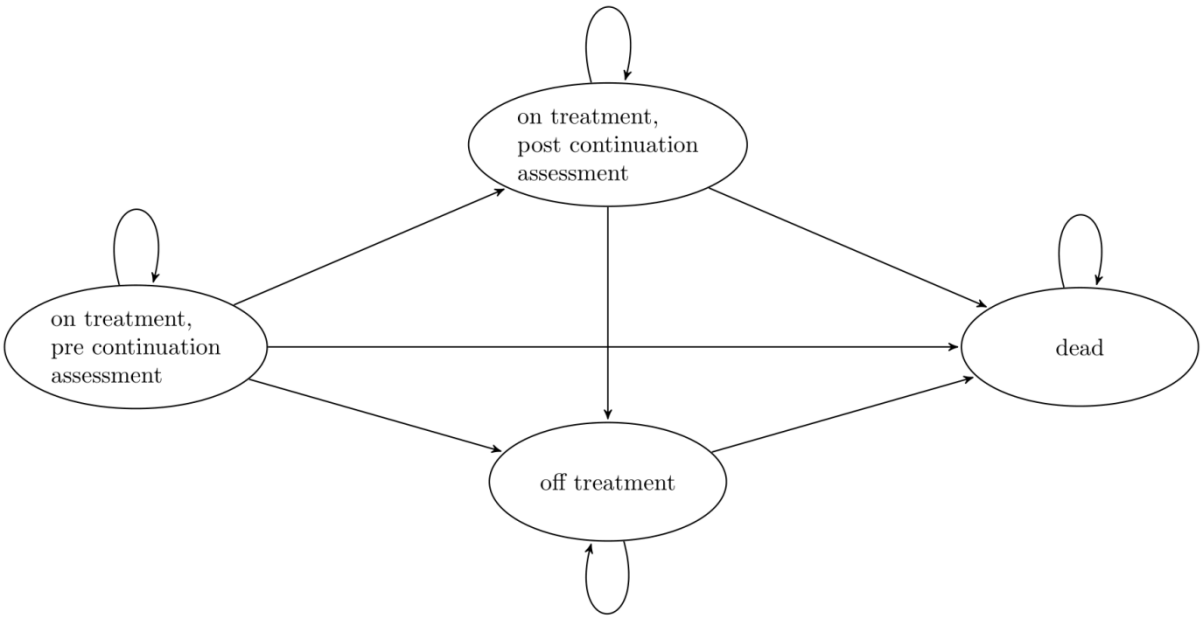
5.2.5 Model structure

The model provided by the company is a Markov cohort model constructed in Microsoft Excel©. A schematic of this model is provided in Figure 10. Patients enter the model with a diagnosis of severe eosinophilic asthma despite best SoC (high dose ICS and additional maintenance treatment or mOCS). The company's model consists of four health states: (i) on treatment pre-continuation

assessment; (ii) on treatment post-continuation assessment; (iii) off treatment; and (iv) dead. Patients in the mepolizumab and omalizumab arms enter the model in the 'on treatment pre-continuation assessment' health state. Patients remain in this state until continuation assessment, which occurs at 12 months for mepolizumab and at 16 weeks for omalizumab. After continuation assessment, patients transition to the 'on treatment post-continuation assessment' state if they meet the continuation criteria for their respective treatment or to the 'off treatment' state otherwise. Grammatically this should be a continuation criterion but we have used continuation criteria to be consistent with the CS. Patients in the 'on treatment post-continuation assessment' state remain in that state until treatment discontinuation or death. Treatment discontinuation might happen either due to natural attrition or by reaching the end of the treatment duration, which in the base case is assumed to be ten years. Patients on the 'off treatment' state remain in that state until death. 'Dead' is an absorbing state. Patients receiving SoC are assumed to start in the off-treatment health state and remain in that state until death.

Patients in the alive states, i.e. all states except 'dead', might suffer clinically significant exacerbations, which can be of three different types: (i) exacerbations requiring treatment with OCS; (ii) a visit to the ED, or; (iii) hospitalisation. Exacerbations are not treated as separate health states, but as transient events occurring within the broad asthma health states. The rate of clinically significant exacerbations is dependent upon the state and the treatment. These rates have been calculated from MENSA for mepolizumab and SoC and through a NMA for omalizumab. The distribution of the exacerbation types is assumed independent of the current state and treatment arm and is calculated based on their incidence in the MENSA trial for each of the populations considered. Each type of exacerbation results in a utility decrement and a cost. Patients who suffer a clinically significant exacerbation have a probability of dying from asthma-related causes. In addition to asthma-related mortality, patients in the alive states may die of other causes transition during any cycle. Transitions to dead, both for general mortality and asthma related mortality are age-dependent.

Figure 10: State transition diagram of the model



5.2.6 Treatment effectiveness and extrapolation

Within the health economic model, treatment effectiveness was modelled through the inclusion of treatment-dependent clinically significant exacerbation rates. Data on the effectiveness of mepolizumab compared with SoC were taken from the MENSA trial.[24] Exacerbation rates for patients in the placebo arm and mepolizumab arms were calculated dividing the total number of exacerbations by the person-years of exposure to obtain an annual rate for each treatment arm. Table 50 shows the annual clinically significant exacerbation rates and the respective 4-weekly rates used in the model for the three considered populations. The ERG noted that slight errors were introduced when calculating all the 4-weekly rates used in the model by assuming a year has 364 days (52 weeks) instead of 365.25; these errors are unlikely to affect the conclusions of the analysis.

After the treatment continuation assessment, the mepolizumab cohort is divided into two groups: those patients who meet the treatment continuation criteria and those who do not. The continuation criteria differs across treatments: patients on mepolizumab continue on treatment unless the exacerbation rate worsens whilst patients on omalizumab continue only if they achieve a physician-rated global evaluation of treatment efficacy score of good or excellent. The proportion of patients meeting the continuation criteria for mepolizumab in each population was taken from the MENSA

trial and is shown in Table 49. The proportion of patients meeting the continuation criteria for omalizumab was assumed to be 56.5% as reported in the INNOVATE[11] trial.

Table 49: Proportion of patients meeting the continuation criteria in MENSA

	ITT population	GSK PP excl. stable mOCS	GSK PP
Total patients	385	102	143
Patients meeting CC	350	99	132
Patients meeting CC (%)	90.9	97.1	92.3

CC = continuation criteria

The exacerbation rate used in the model for those patients who meet the continuation criteria was calculated using a negative binomial model, using the data from Week 16 to end of study (Week 32) from patients meeting the continuation criteria in MENSA. This rate was applied for these patients for the rest of the treatment. The ERG notes that this is not ideal for three reasons. Firstly, fluctuations in the number of exacerbations for an individual could mean that the future rates of asthma exacerbations observed in patients who met the continuation criteria (which was a non-worsening of the exacerbation rate from the start of the treatment to continuation assessment) is likely to be higher than the values used due to regression to the mean. Secondly, the exacerbation rate is measured during a short period (16 weeks), which results in an uncertainty and potential inaccuracy due to the seasonal nature of asthma exacerbations. Thirdly, given that the exacerbation rate is measured shortly after treatment initiation, this may not be representative of its long-term effectiveness. Patients not meeting the continuation criteria at continuation assessment (1 year in the base case) are taken off mepolizumab treatment and are subsequently assumed to experience the same exacerbation rate as those patients in the SoC group. The ERG notes that this assumption is likely to underestimate the exacerbation rate of this subgroup of patients because these were the more severe patients and are likely to have higher rates of exacerbations.

Table 50: Clinically significant exacerbation rates used in the company's model

Comparator	Full Trial Population (ITT of MENSA)		GSK PP excl. stable mOCS		GSK PP	
	Annual rate	4-weekly rate	Annual rate	4-weekly rate	Annual rate	4-weekly rate
SoC	1.744	0.134	3.101	0.239	2.650	0.204
Add-on mepolizumab (pre-CA)	0.877	0.067	1.213	0.093	1.206	0.093
Add-on mepolizumab (post-CA)	0.550	0.042	0.723	0.056	0.645	0.050

CA = Continuation assessment

The company claimed that the distribution of the type of exacerbations did not vary across treatments but did vary by sub-population (see Table 51). The distribution of the different types of exacerbations was calculated from the MENSA trial using data from both treatment arms.

Table 51: Distribution by type of exacerbation used in the model

Type of exacerbation	Full Trial Population (ITT of MENSA)			GSK PP excl. stable mOCS			GSK PP		
	n	N	%	n	N	%	n	N	%
OCS burst	373	449	83.1%	127	166	76.5%	164	210	78.1%
ED visit	39	449	8.7%	18	166	10.8%	22	210	10.5%
Hospitalisation	37	449	8.2%	21	166	12.7%	24	210	11.4%

For the comparison with omalizumab, the company undertook an NMA (described in Section 4.4) to calculate the effectiveness of mepolizumab and omalizumab in the overlap population. The company calculated the exacerbation RRs both for mepolizumab and omalizumab relative to SoC (see Table 52) using a fixed effects model. These RRs are only used in the model to estimate exacerbation rates for patients on mepolizumab and omalizumab until the continuation assessment, which happens after 52 and 16 weeks for mepolizumab and omalizumab, respectively.

Table 52: Rate ratios and 4-weekly rates used in the model before continuation assessment

Comparator	RR vs. Placebo	Upper 95% CrI	Lower 95% CrI	4-weekly rate
Add-on mepolizumab	0.496	0.407	0.603	0.066
Add-on omalizumab	0.746	0.630	0.883	0.101

RR = Rate ratio; CrI = Credible Interval

The results of the NMA were only used before continuation assessment. After continuation assessment, the RRs for patients meeting the continuation criteria reported in INNOVATE and MENSA were used for omalizumab and mepolizumab respectively, as shown in

Table 53. The ERG notes that it would have been more appropriate to use the RR for omalizumab and mepolizumab for patients on mOCS, given that omalizumab is recommended by NICE only for patients who *"need continuous or frequent treatment with oral corticosteroids"*.[11] It is worth mentioning that omalizumab appears to be more effective in this subgroup (RR=0.293),[11] whereas mepolizumab seems to be less effective (based on the data from SIRIUS where the RR is 0.77) although the ERG notes that the NMA uses ITT data for both interventions.

Table 53: Rate ratios and 4-weekly rates used in the model after continuation assessment

Comparator	RR vs. Placebo	4-weekly rate	Source
Add-on mepolizumab	0.316	0.042	MENSA[24]
Add-on omalizumab	0.373	0.050	INNOVATE[11]

RR = Rate ratio

The ERG notes that whilst the correct values are used in the model, the company appears to have erroneously reported the 4-weekly rates for the GSK PP in Tables 106 and 107 of the CS.

5.2.7 Mortality

The company's model assumes that asthma-related mortality occurs only following a clinically significant exacerbation. In the base case analysis, the mortality rates after clinically significant exacerbations were based on two sources: Watson *et al*.[1] and the NRAD report.[22]

The study by Watson *et al*.[1] was the only study identified in the CS to report mortality rates for patients hospitalised for acute severe asthma stratified by age band. A further source of asthma-related mortality was Roberts *et al*,[2] however, the company claimed that these mortality rates were for a general asthma population rather than for severe asthma and was thus likely to underestimate the mortality in the target population.

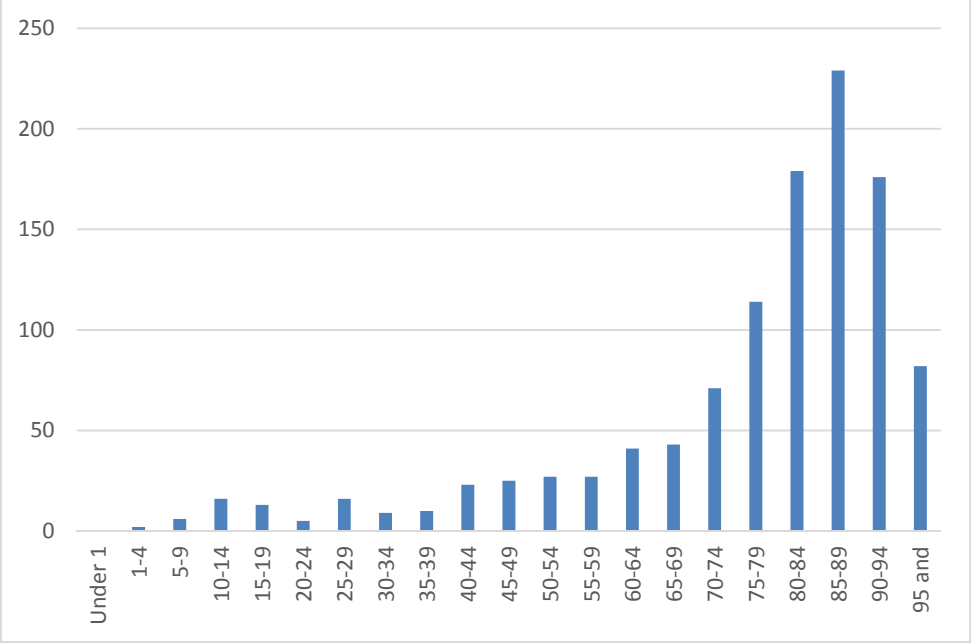
The ERG notes that the age stratification in Watson *et al*.[1] fails to capture the increase of asthma-related mortality rates observed after the age of 45. In Roberts *et al*.[2] patients above the age of 45 are stratified into three ranges (45–54 years; 55–64 years; and 65 years and over) and the mortality rate for patients 65 years and over is roughly six times higher than the rate in the age range 45-54 years. The ERG notes that assuming a constant mortality rate after the age of 45 years is therefore likely to overestimate the mortality at a younger age, thus favouring mepolizumab in the base case where the model start age is assumed to be 50.1 years. Table 54 shows the mortality rates after an asthma-related hospital admission stratified by age.

Table 54: Mortality rates after hospital admission stratified by age

Age group	Watson *et al*.[1]	Roberts *et al*.[2]
18-24	0.0038	0.0015
25-34		0.0014
35-44		0.0020
45-54	0.0248	0.0045
55-64		0.0127
≥65		0.0278

Figure 11 shows the deaths caused by asthma registered in England and Wales in 2014 stratified by age as reported by the Office for National Statistics.[48] These data confirm that asthma-related mortality increases markedly after the age of 65 years with 80% of the asthma-related deaths occurring in people aged 65 years or older.

Figure 11: Asthma deaths in England and Wales, 2014. Source: Office for National Statistics[48]



The NRAD report analyses 195 asthma-related deaths. The categories of locations of death within the NRAD report were: home (private address) 41%; hospital, arrest in hospital 30%; hospital, pre-hospital arrest 23%; nursing / residential home 3%; holiday 2%; and other 1%.

The company's model assumes that all deaths in Watson *et al*. would be categorised as 'hospital, arrest in hospital', which account for the 30% of deaths in the NRAD report, and that therefore the total number of deaths would be 100/30 times greater than those reported in Watson *et al*. These additional deaths were divided between those exacerbations that required an ED visit (23/70) and those assumed to only require an OCS burst (47/70). The distribution of deaths amongst the three groups of exacerbations: hospitalisation; ED visit and OCS burst were assumed constant and

independent of the number of deaths reported in hospital. The ERG notes that should any of the deaths in Watson *et al*. be assignable to the 'hospital, pre-hospital arrest' category, then the number of deaths due to asthma exacerbations would be overestimated.

Finally, the CS used as a scenario analysis the mortality rate used in the recent NICE Multiple Technology Appraisal (MTA) for omalizumab,[11] that is, the midpoint between Watson *et al*.[1] and de Vries *et al*.[49] incremented by 15% to account for the extreme severity of asthma of the target population. In the MTA for omalizumab the mortality rates after hospitalisation reported by Watson *et al*.[1] were assumed to be equal to mortality rates after any type of clinically significant serious exacerbations. The ERG notes that this assumption was likely to overestimate asthma-related mortality. The ERG also notes that the type of exacerbations considered in the omalizumab MTA within the Single Technology Appraisal (STA) of mepolizumab differed and thus so did their frequency in the SoC treatment arm (annual rates of 0.885 and 1.744 respectively used in the ITT populations for the omalizumab and mepolizumab appraisals respectively). Therefore, the ERG notes that using the same approach to model asthma-related mortality as in the omalizumab MTA was of limited validity.

5.2.8 Health related quality of life

EQ-5D scores were captured at 4-weekly intervals in the DREAM trial but not for the MENSA and SIRIUS trials, where SGRQ was used. The model uses EQ-5D scores mapped from the SGRQ scores measured in the MENSA trial rather than the direct EQ-5D data within DREAM. The mapping from SGRQ scores to EQ-5D scores was performed using an algorithm proposed by Starkie *et al*.[50] to predict EQ-5D utility from the SGRQ in subjects with COPD: it is uncertain to what extent the mappings obtained using data from COPD rather than asthma could influence the results.

The company justified the use of mapping claiming "EQ-5D did not capture the granularity in HRQL of people with severe asthma", based on two phenomena observed in the EQ-5D scores recorded in DREAM: a third of the severe asthma patients reported a utility of 1.0 thus making any improvement as a result of mepolizumab therapy impossible; and the EQ-5D differential between mepolizumab and SoC was smaller in patients experiencing ≥ 4 exacerbations in the previous 12 months than in the ITT population. The ERG and its clinical advisors were not surprised by the proportion of people with an EQ-5D score of 1.0 as the EQ-5D evaluates utility at the moment at which the questionnaire is completed and does not use a recall period, meaning that if a patient's asthma was controlled and the underlying symptoms did not cause any problems or moderate symptoms on any of the five domains (mobility; self-care; usual activities; pain / discomfort; and anxiety / depression) then the patient would receive a score of 1.0.

In contrast, the SGRQ has a recall period that can be up to 1 year in duration, although a 3-month recall period version is available. The CS was not explicit about the recall period used but were not asked about this in the clarification process. As such, the SGRQ will be more sensitive to asthma-related events (such as exacerbations or hospitalisations) that occurred within the previous 3 to 12 months than the EQ-5D. However, the ERG noted that if the mapping procedure predicted the EQ-5D correctly from the SGRQ, the resultant values would suffer from the same problems described by the company as the EQ-5D does. In response to a request for clarification on this matter (question B9), the company argued that the HRQoL measured using the SGRQ "seemed more akin to clinical practice" because it did not suffer from the same ceiling effects as the EQ-5D. The company also mentioned that it had included a scenario analysis using directly measured EQ-5D in the CS and that the resulting ICER still remained under "an acceptable cost-effectiveness threshold." The ERG's views on the appropriateness of mapped SGRQ values are discussed later.

Table 55 shows directly measured EQ-5D scores and SGRQ-mapped scores used for patients in the three alive states of the model dependent on their treatment. The company's base case analysis uses the SGRQ-mapped scores. The company assumed that patients on omalizumab would benefit from the same HRQL as those on mepolizumab.

Table 55: Directly measured EQ-5D scores and SGRQ-mapped utility scores (and their standard error (SE))

	ITT population		GSK PP excl. stable mOCS		GSK PP	
	EQ-5D	SGRQ-mapped	EQ-5D	SGRQ-mapped	EQ-5D	SGRQ-mapped
Mepolizumab: before CA	0.802 (0.005)	0.796 (0.010)	0.829 (0.009)	0.793 (0.021)	0.827 (0.007)	0.777 (0.017)
SoC treatment†	0.794 (0.005)	0.738 (0.015)	0.797 (0.011)	0.682 (0.038)	0.785 (0.009)	0.708 (0.029)
Mepolizumab: after CA	0.824 (0.006)	0.806 (0.009)	0.834 (0.012)	0.805 (0.018)	0.837 (0.009)	0.795 (0.016)

CA = continuation assessment †Regardless of whether patients had prior mepolizumab

Decrements in HRQoL associated with an exacerbation reported by Lloyd *et al*.[51] were assigned to exacerbations requiring a burst of OCS and exacerbations requiring hospitalisation. Since Lloyd *et al*. did not report the disutility estimated for exacerbations requiring a visit to the ED, the company assumed that this was equal to the disutility for an exacerbation requiring OCS. Table 56 shows the utility decrements assigned in the model to the different exacerbation types and their source.

Table 56: Utility decrements assigned to different exacerbation types

Exacerbation type	Utility decrement	Source
OCS burst	-0.10	Lloyd *et al.*[51]
ED visit	-0.10	Assumption
Hospitalisation	-0.20	Lloyd *et al.*[51]

The company noted that there could be double counting with respect to the use of the SGRQ. The CS states the following (p210): *"It should also be noted that there is an element of double counting which cannot be accounted for. The utility as derived from SGRQ theoretically captures disutility associated with an exacerbation, since instrument items ask patients to retrospectively capture their HRQL (i.e. beyond the moment when the instrument is administered). However it does not explicitly capture the HRQL impact of an exacerbation event. Again, this approach is no different than that utilised in the omalizumab NICE MTA.[11]"* The level of the double counting will be dependent of the accuracy of the mapping from the SGRQ to the EQ-5D: if the mapping was accurate then it is possible that there would be no double counting.

The CS states that adverse reactions were not included in the model due to the small proportions of events and minor differences between treatment groups.

5.2.9 Resources and costs

The company's model takes into account drug acquisition costs, administration costs, monitoring costs and costs associated with managing exacerbations. Standard of care drug costs, which included a combination of ICS/LABA, short-acting beta agonists (SABA), anti-leukotriene, theophyllines and OCS, were applied to patients in all states except dead. The cost of mepolizumab per cycle was assumed to be equal to the price of a 100mg mepolizumab vial, as it is administered once every four weeks. The cost of omalizumab is more complicated to calculate, as the dosage is dependent on the patient's weight and their IgE level. In order to calculate the average annual cost of omalizumab per patient, the company undertook a study to measure the dosing distribution of omalizumab in patients over 18 years of age in the secondary care setting in England for the years 2010-2014. This study resulted in an estimated annual cost of £11,370 (£872.22 per cycle) per person; this is notably higher than the £8,056 (£617.99 per cycle) reported in the assessment report of the recent NICE MTA for omalizumab.[11] The former cost was used in the base case analysis and the latter cost in a scenario analysis. Table 57 shows a summary of mepolizumab and omalizumab acquisition costs per cycle. All analyses presented in this document where undertaken using the PAS price of mepolizumab and the list price of omalizumab. The ERG performed these same analyses with the PAS prices of mepolizumab and omalizumab and presented these results in a confidential appendix.

Table 57: Mepolizumab and omalizumab acquisition costs per cycle

Drug	Cost/Unit (excluding VAT)		Source
	List price	PAS price	
Add-on mepolizumab	£840	[redacted]	GSK
Add-on omalizumab	Base case: £872.22	[redacted]	GSK study
	Scenario analysis: £617.99	[redacted]	NICE MTA 2013[11]

GSK: GlaxoSmithKline; PAS: Patient Access Scheme

Two consultant-led outpatient attendances per year were assumed for patients in each treatment group. All administrations for a biologic therapy are assumed to be undertaken by a specialist asthma nurse, based on an assumed administration time of 10 minutes, at a cost of £16.67. The costs of conducting tests to determine blood eosinophil levels and IgE levels have not been included as the company states that these tests are already conducted at routine attendances for severe asthma patients. Patients receiving omalizumab or mepolizumab are assumed to be monitored post-administration for one hour, involving 15 minutes of specialist nurse time.

Exacerbation costs were calculated based on resource utilisation in the MENSA and DREAM trials. The unit costs for these resources were taken from various sources and are summarised in

Table 58. The cost of hospitalisation was calculated as a weighted average using all asthma-related hospitalisation codes and their relative frequencies.

Table 58: Unit costs for resources used for exacerbation resolution

Resource	Cost	Source
Telephone call	£28.00	PSSRU 2014[52]
Home day visit	£46.00	PSSRU 2014[52]
Home night visit	£46.00	Company assumption
Practice Visit	£67.00	PSSRU 2014[52]
Outpatient attendance	£149.58	NHS Reference costs 2013 to 2014;[53] Service code 340 Respiratory Medicine
OCS – prednisone per mg	£0.01	BNF 2015[54]
Emergency room attendances	£123.67	NHS Reference costs 2013 to 2014;[53] Weighted Average from multiple emergency medicine codes
Hospitalisation	£1,277.59	NHS Reference costs 2013-13;[53] currency codes DZ15G, DZ15H, DZ15J, DZ15K, DZ15L

PSSRU = Personal Social Services Research Unit; BNF = British National Formulary

5.2.10 Cost effectiveness results

All analyses have been undertaken using the mepolizumab PAS

5.2.10.1 Mepolizumab add-on vs. standard of care

The CS reports the deterministic and probabilistic results for the base case analysis, including estimated QALYs, costs, and resulting ICERs for each treatment and population. These are reproduced in

Table **59**. Probabilistic ICERs ranged from £15,478 to £31,692 based on the chosen population with a range in the QALYs gained of [redacted] to [redacted].

Table 59: Results of the base case analysis comparing mepolizumab with SoC, showing discounted QALYs and costs

	ITT population			GSK PP excl. stable mOCS			GSK PP		
	Mepo	**SoC**	**Mepo vs. SoC**	**Mepo**	**SoC**	**Mepo vs. SoC**	**Mepo**	**SoC**	**Mepo vs. SoC**
Deterministic results									
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			**£31,659**			**£15,394**			**£19,526**
Probabilistic results									
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			**£31,692**			**£15,478**			**£19,511**

Table 60 shows the probability of mepolizumab being cost-effective compared to standard of care at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, for the three analysed populations.

Table 60: Probability mepolizumab is cost-effective compared with SoC at different willingness-to-pay per QALY gained

Willingness to pay per QALY gained	**ITT population**	**GSK PP excl. stable mOCS**	**GSK PP**
£20,000	0.0005	0.9325	0.562
£30,000	0.352	0.9995	0.985

5.2.10.2 Mepolizumab add-on vs. omalizumab add-on

The CS reports the results of the base case analysis comparing mepolizumab to omalizumab (see Table 61). This analysis concludes that mepolizumab dominates omalizumab due to its superior effectiveness ([redacted] extra QALYs) and lower price ([redacted] cheaper than omalizumab). However, the validity of these results is limited, given that list price for omalizumab was used instead of the approved PAS (due to its confidential nature). The estimated ICER for mepolizumab compared with standard of care derived from the NMA is consistent with the estimate calculated using the data from MENSA (£31,672 and £31,692 respectively).

Table 61: Results of the base case analysis comparing mepolizumab with omalizumab (list price) showing discounted QALYs and costs

	Mepo	Omalizumab	Mepo vs. omalizumab	SoC	Mepo vs. SoC
Deterministic results					
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			**Dominant**		**£31,618**
Probabilistic results					
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER			**Dominant**		**£31,672**

5.2.11 Sensitivity analyses

5.2.11.1 Univariate sensitivity analyses

The company performed a number of univariate sensitivity analyses to test the robustness of the model to changes in the values of various input parameters. The CS includes four tornado diagrams, each showing how the ICER varies when the value of key model parameters is varied within the limits of their 95% confidence interval. The tornado diagram in

Figure 12 shows that the ICER for mepolizumab versus SoC for the GSK PP excl. stable mOCS is lower than £20,000 per QALY gained in all univariate analyses. In contrast, the tornado diagram in Figure 13 shows that the ICER for mepolizumab versus SoC for the GSK PP becomes greater than £20,000 per QALY gained when the value of the 95% confidence interval least favourable to mepolizumab is used for many key parameters: namely utility values and exacerbation rates, as well as the mortality rate after exacerbation. The tornado diagram in

Figure 14 shows that mepolizumab consistently dominates omalizumab at the limit of the 95% confidence interval for all parameters. The tornado diagram in
Figure 15 shows that the NMA derived ICER for mepolizumab against SoC for the GSK PP becomes greater than £20,000 per QALY gained when the value of the 95% confidence interval least favourable to mepolizumab is used for key parameters.

Figure 12: ICER of mepolizumab versus SoC alone; GSK proposed population excluding mOCS users with <4 exacerbations (reproduced from CS Figure 33)

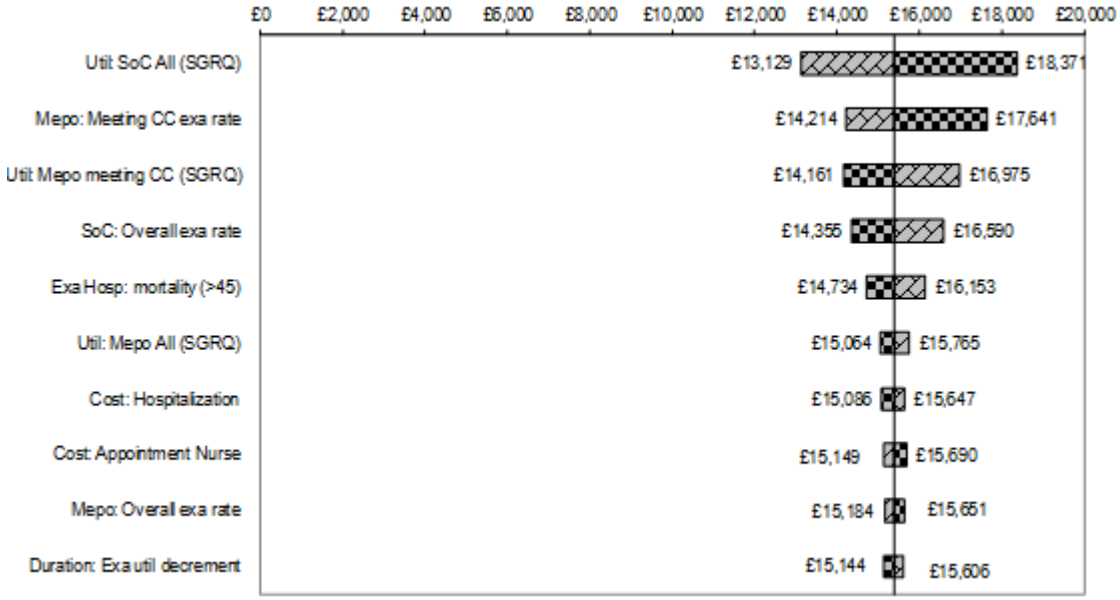


Figure 13: ICER for mepolizumab versus SoC alone; GSK proposed population (reproduced from CS Figure 34)

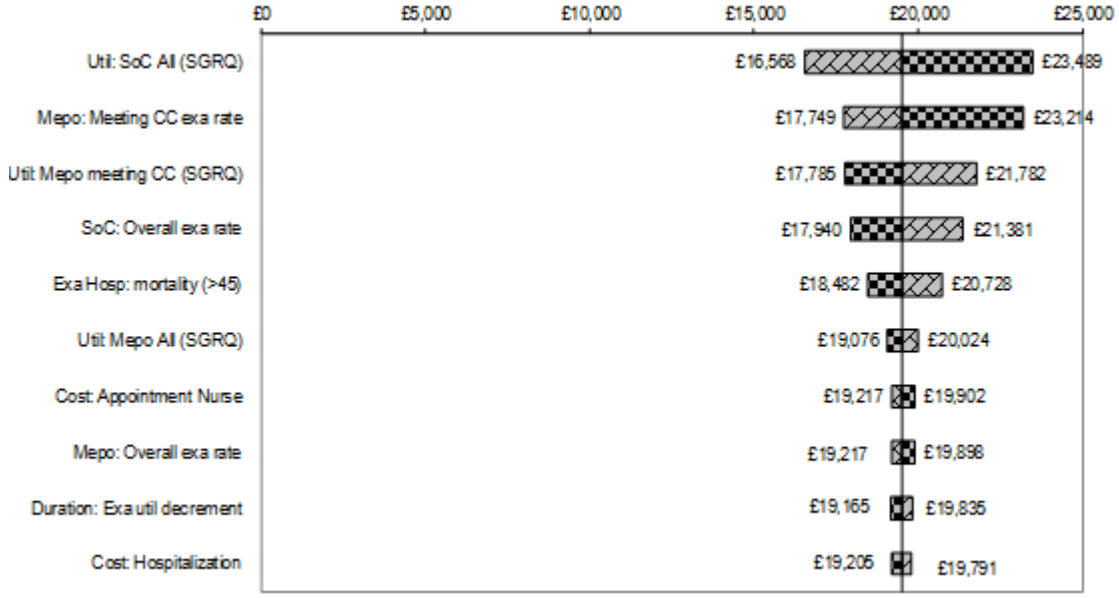


Figure 14: ICER mepolizumab versus omalizumab; Full ITT (reproduced from CS Figure 35)

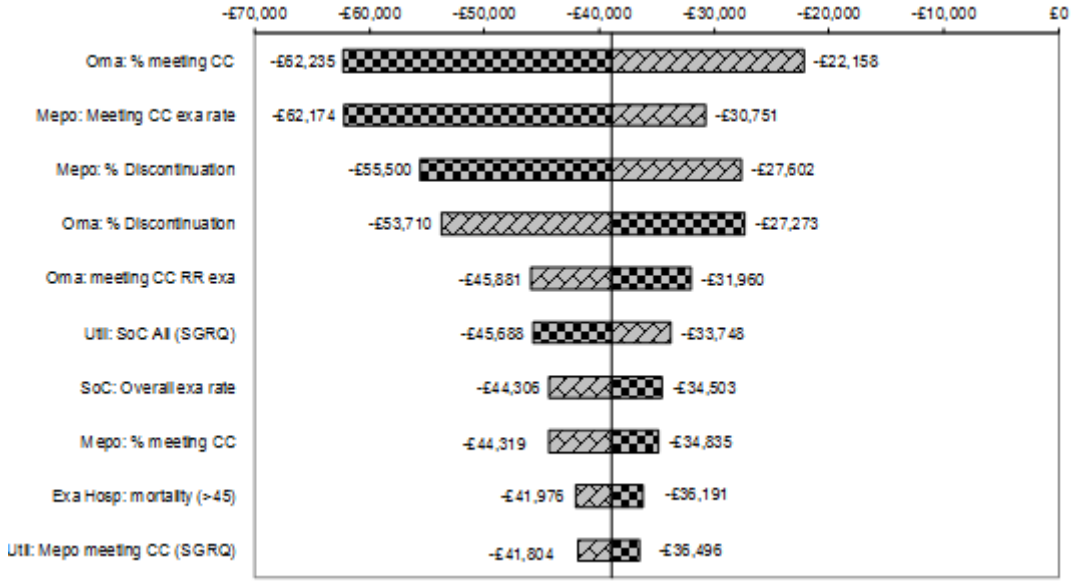
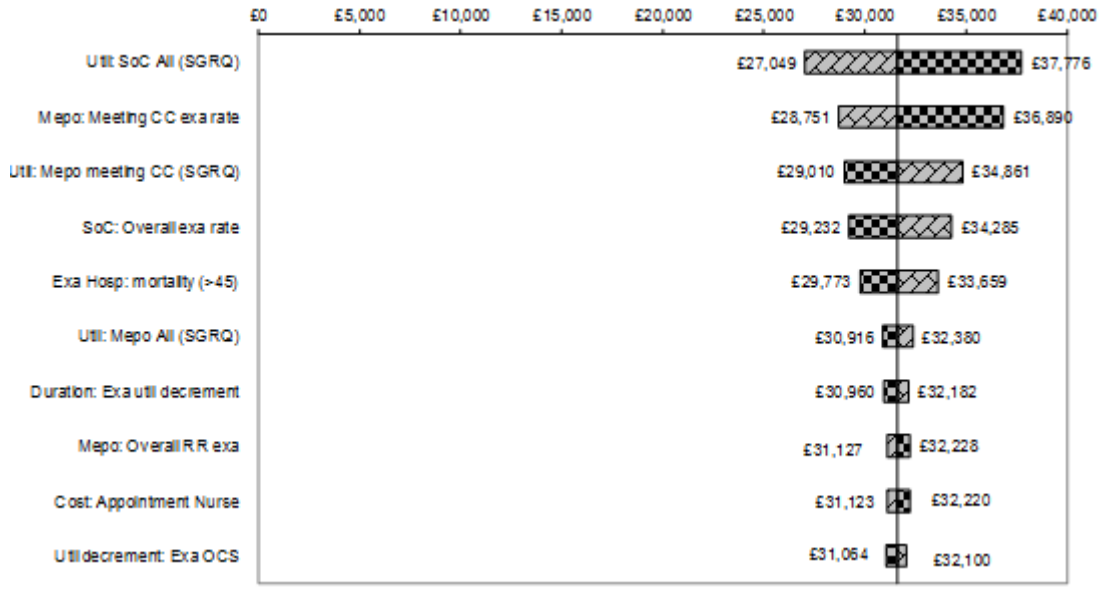


Figure 15: ICER mepolizumab versus SoC alone; Full ITT (reproduced from CS Figure 36)



5.2.11.2 Scenario analyses

The company performed a series of scenario analyses to test how some of the assumptions of the model affected the ICER. The results of the scenario analyses for the comparison between mepolizumab add-on and SoC are reported in Table 147 of the CS (p224-245); selected analyses are reproduced in Table 62.

Table 62: Selection of scenario analyses for mepolizumab compared to SoC

	GSK PP excl. stable mOCS					GSK PP				
	Total cost (£)	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (£)**	**Total cost (£)**	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (£)**
Base case										
Mepo	[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	15,394	[redacted]	[redacted]	[redacted]	[redacted]	19,526
Age at baseline: 30 years										
Mepo	[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	25,289	[redacted]	[redacted]	[redacted]	[redacted]	35,055
Age at baseline: 65 years										
Mepo	[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	17,384	[redacted]	[redacted]	[redacted]	[redacted]	22,705
Biologic treatment duration: Life time										
Mepo	[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	15,571	[redacted]	[redacted]	[redacted]	[redacted]	19,763
Source of asthma related mortality: Watson 2007 (No NRAD)										
Mepo	[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	21,850	[redacted]	[redacted]	[redacted]	[redacted]	29,833
Source of asthma related mortality: Roberts 2013										
Mepo	[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	23,211	[redacted]	[redacted]	[redacted]	[redacted]	31,680
Source of asthma related mortality: Roberts 2013 (No NRAD)										
Mepo	[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	27,795	[redacted]	[redacted]	[redacted]	[redacted]	39,396
Source of health state utilities: EQ-5D (DREAM)										
Mepo	[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	18,429	[redacted]	[redacted]	[redacted]	[redacted]	20,863
Source of duration of utility decrement for an exacerbation: MENSA										
Mepo	[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	15,690	[redacted]	[redacted]	[redacted]	[redacted]	19,963

Discontinuation beyond year 1: 0%										
Mepo										
SoC					15,305					19,326
Discontinuation beyond year 1: 20%										
Mepo										
SoC					15,516					19,792

The first two scenario analyses show how the ICER changes when the age at baseline is changed to 35 years and 65 years (base case age at baseline= 50.1 years). The analyses show that the ICER is increased when the average age is decreased and that the ICER is also increased when the average age is increased. This suggests that there is a parabolic relationship between the ICER and the average age, with younger patients having a lesser mortality risk following an exacerbation and with older patients having less years to live following prevention of an asthma-related mortality (ARM) through the use of mepolizumab.

The company's base case assumes the treatment duration to be ten years. However, the clinical advisors to the ERG stated that they saw no reason to stop an effective treatment after ten years (as assumed in the base case) and therefore a lifetime duration of mepolizumab may be more plausible. The ICER under this assumption is very similar to that of the base case, as the model assumes constant costs and effectiveness.

Scenario analyses used different sources to estimate the rates of ARM after exacerbation. Assuming all deaths occurred within hospital, the ICER increases from £19,526 to £29,833 per QALY gained compared with SoC for the GSK PP and from £15,394 to £21,850 per QALY gained for the GSK PP excl. stable mOCS. These results confirm that the rates of ARM are a key driver of the cost-effectiveness of mepolizumab. If mortality rates after hospitalisation reported by Roberts *et al*.[2] are used in the model instead of Watson *et al*.,[1] the ICER also increases substantially to £31,680 per QALY gained for the GSK PP and to £23,211 per QALY gained for the GSK PP excl. stable mOCS. Roberts *et al*.[2] is deemed an inappropriate source by the company because it does not specifically report mortality for severe asthma but reports it for all asthma patients instead. The ERG acknowledges that this is likely to underestimate ARM and thus be unfavourable to mepolizumab but notes that the data from Roberts *et al*.[2] account for the increase in mortality rates after the age of 45 years whereas those from Watson *et al*.[1] do not. When deaths outside of hospital are excluded and Roberts *et al*.[2] is used as the source of rates of ARM, the ICERs increase further to £39,396 and

£27,795 per QALY gained compared with SoC for the GSK PP and the GSK PP excl. stable mOCS, respectively.

The source of the utilities used in the model has a moderate effect on the ICER. When using the EQ-5D scores captured in DREAM, rather than SGRQ captured in MENSA mapped to EQ-5D, the ICER increases from £19,526 to £20,863 in the GSK PP and from £15,394 to £18,429 per QALY gained in the GSK PP excl. stable mOCS. When the source for the length of utility decrement caused by exacerbations was taken from MENSA, rather using the four-week assumption based on Lloyd *et al*.,[51] there was a small increase in the ICER.

The ICER was relatively robust to the assumed percentage of annual discontinuation, with values of 0% and 20% providing similar ICERs to that in the base case (rate=10%).

The company performed scenario analyses for the comparison between mepolizumab and omalizumab; these are summarised in the Table 148 in the CS (p246-248). In all analyses, mepolizumab dominated omalizumab, however, these results are based on the list price for omalizumab rather than the commercial-in confidence PAS price.

5.2.11.3 Scenario analysis: OCS sparing

The company performed a scenario analysis that attempted to include long-term costs and consequences of maintenance OCS. For that purpose, the company undertook a study using the Clinical Practice Research Datalink (CPRD) to estimate the dose-dependent risk of developing 6 AEs associated with systemic corticosteroid therapy: myocardial infarction; glaucoma; diabetes; cataracts; osteoporosis; and peptic ulcer.

The company used the data collected during SIRIUS to calculate the reduction in OCS use in two ways: using the percentage of patients that managed a total reduction of OCS and the median percentage of OCS reduction. The company stated that the median was used instead of the mean due to the skewedness of the distribution, although the ERG notes that it is typical to use mean values in economic evaluations. The ERG notes that using the percentage of patients that had managed to discontinue OCS treatment was likely to underestimate the OCS dose reduction. The ERG considers that it would have been more appropriate to use population-dependent data instead of assuming that the reductions in OCS use and the proportion of patients on mOCS in the ITT population was applicable for all three populations. The company assumes that the OCS reduction data gathered in SIRIUS are applicable for omalizumab. The ERG notes that data relating to the proportion of patients discontinuing OCS are available in the Assessment Group's report for the omalizumab MTA and are

markedly different from those for mepolizumab: 14.5% of patients discontinued OCS treatment in SIRIUS compared with 41.9% of omalizumab responders).[45]

The time horizon used to calculate the costs and consequences of AEs associated with systemic OCS was 10 years, matching the biologic treatment duration in the base case analysis. The ERG notes the use of a time horizon shorter than lifetime is likely to underestimate the benefits of OCS sparing, as some of the diseases avoided during the treatment are chronic and therefore would have been suffered by the patients for the rest of their lives, or these diseases could develop or become symptomatic beyond the 10-year time horizon.

The company uses data from MENSA to calculate exacerbation rates in mepolizumab patients in addition to using the OCS usage reduction data from SIRIUS. The ERG notes that this, in isolation, is likely to overestimate the aggregate benefits of mepolizumab, as exacerbation rates might not decrease as much when reducing OCS usage.

It is unclear how the annual cost of osteoporosis was calculated, but it was estimated to be much lower than the cost to treat fractures estimated by Manson *et al*.,[55] the source used in the omalizumab MTA. In Manson *et al*.[55] fractures account for the 80% of the cost associated to AEs resulting from long term OCS sparing compared with 0.2% in the CS. However, despite this, the aggregated cost of the AEs per patient on systemic OCS per year is estimated to be £222 by the company, compared with £165 estimated by Manson *et al*.[55] (valued at 2007 prices). The value from Manson *et al* is estimated to be £188 in 2014/2015 using the hospital and community health services index values reported in Curtis and Burns.[56]

The ERG notes that the model uses the EQ-5D scores reported by Sullivan *et al*.[57] as if they were one-off disutilities in the case of cataracts, MI, and peptic ulcer. This is likely to under-estimate the utility loss associated with these chronic diseases.

The probability of suffering an AE in each cycle was not multiplied by the proportion of the cohort that was alive in that cycle; this is likely to overestimate the total incidence of AEs. Also, the percentage of the cohort that suffered chronic AEs (diabetes and osteoporosis) in each cycle (described as "cumulative probability" in the model) was overestimated since the probability of death was ignored.

As shown in Table 63, considering the costs and consequences of long term systemic OCS does not have a noticeable impact on the ICER, using either of the two OCS reduction calculation approaches. These results were contrary to the prior beliefs expressed by clinical advisors to the ERG that mOCS

use was associated with significant disease burden who anticipated seeing a greater reduction in the ICER.

Table 63: ICERs for the scenario analyses including long-term costs and consequences of systemic OCS (as reported in the CS)

	ITT	GSK PP excl. stable mOCS	GSK PP
Base case	£31,659	£15,394	£19,526
Median dose reduction approach	£31,608	£15,375	£19,500
Total discontinuation approach	£31,649	£15,391	£19,522

5.2.11.4 Sensitivity analyses performed in response to clarification questions raised by the ERG

The ERG noted that the comparison between the ICERs for the GSK PP and the GSK PP excl. stable mOCS suggests that there is a subgroup (mOCS users with <4 exacerbations) included in the GSK PP. This subgroup accounts for approximately 30% of the GSK PP in the MENSA trial and as stated by GSK *"this population will appear less cost-effective compared to the GSK proposed population when excluding mOCS users who did not achieve the required 4 exacerbations in the previous year, despite representing a more severe population."* During clarification, the ERG requested that a separate analysis be performed to estimate the ICER for the use of mepolizumab in mOCS users with a blood eosinophil count of ≥150 cells/μL at initiation of treatment and <4 exacerbations (question B1). The company performed the requested analysis and reported an ICER of £78,716 per QALY gained (see Table 64). The increase in the ICER was due to: (i) a lower exacerbation rate; (ii) fewer exacerbations requiring hospitalisation (and therefore lower asthma related mortality), and; (iii) and a smaller difference in the utilities between mepolizumab and the comparator in this subgroup.

Table 64: Results of the subgroup analysis for mOCS users with a blood eosinophil count of ≥150 cells/μL at initiation of treatment and <4 exacerbations

	Total Cost	Δ Cost	Total QALY	Δ QALY	ICER (vs.)
Mepolizumab + Standard of Care	[redacted]	-	[redacted]		
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	£78,716

The ERG was also concerned that the age stratification of asthma related mortality rates in Watson *et al.*[1] could lead to an overestimation of deaths due to asthma in the early years within the model. In reply to the ERG's clarification letter, the company performed two exploratory analyses combining the asthma-related mortality rates reported by Watson *et al.*[1] and Roberts *et al.*,[2] using two different

approaches: by applying the rate ratios derived from comparing the rate for the 35-44 age band with the other age bands as reported by Roberts *et al*. to the mortality rate reported by Watson *et al*. for the 17-44 age band (option 1); and assuming the same number of exacerbations across the three age bands and fitting the total deaths reported by Watson *et al*. in a way that the relative RRs of the different age bands were similar to those reported by Roberts *et al*. (option 2). The ERG preferred option 2: the resultant assumed mortality rates using this approach are shown in Table 65.

Table 65 Mortality rates calculated based on the number of deaths and hospitalizations reported for the ≥45 group in Watson *et al.*[1] and the ratios in Roberts *et al.*[2] (option 2)

Age group	**Roberts *et al.*[2]**		**Watson *et al.*[1]**			**Watson *et al.*[1] + Roberts *et al.*[2]**			
	p	ratio	p	n	N	p	ratio	n	N
45-54	0.0045		0.0248	177	7143	0.0076		18	2381
55-64	0.0127	2.84				0.0214	2.83	51	2381
≥65	0.0278	6.20				0.0454	6.00	108	2381

The ERG considers that the exacerbation rates used in the model for patients who meet the continuation criteria could be inappropriate: these rates were measured in the MENSA trial shortly after the beginning of the treatment, based on a 16-week time span and therefore might not be representative of the long-term effectiveness of mepolizumab and may be affected by seasonality; further, there may be a regression to the mean. In contrast, in the COSMOS study, the rates were measured in a period of a full year in patients that had already been on mepolizumab for 32 weeks. The company acknowledged in their clarification responses (question A19) that the continuation criteria in COSMOS were consistent with recommendations in the SmPC. Additionally, the percentage of MENSA patients that went on to participate in COSMOS is almost identical to those meeting the continuation criteria in the ITT population of MENSA (90.1% vs 90.9%). For these reasons, during the clarification process, the ERG requested the company to undertake an analysis whereby exacerbation rates from COSMOS were used in the model as exacerbation rates for patients on mepolizumab who met the continuation criteria (question B4). However, the company did not undertake the requested analysis and argued instead that the exacerbation rate measured in COSMOS in patients who had been treated with mepolizumab during MENSA (rate=0.9) was similar to that measured in the ITT population in MENSA (rate=0.877). The ERG agreed in the similarity of these two rates but note that they are markedly different to the rate used in the model for patients on mepolizumab meeting the continuation criteria (rate=0.55 in the ITT population).

The ERG also requested a scenario analysis based on the exacerbation rates and utilities recorded in the DREAM trial and analyses where exacerbation rates were calculated through a meta-analysis of data gathered in MENSA and DREAM, both using EQ-5D utilities (DREAM) and the SGRQ-mapped utilities (MENSA).

The ERG believes that the results of the SIRIUS trial are particularly relevant, since it assesses the effectiveness of mepolizumab in patients on mOCS. The GINA guidelines[58] specify that "patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered" should be considered in Step 5, which usually entails maintenance OCS. Bousquet *et al.* consider that having more than two exacerbations in a year is sufficient for asthma to be categorised as "poorly controlled".[59] Considering that the patients in the GSK PP that are not on maintenance OCS suffered at least four such exacerbations in the previous year, the ERG believes that the inclusion of mOCS for these patients should have been considered. Therefore, the ERG believes that mOCS is a relevant comparator for the GSK PP in addition to the comparator of usual Step 4 treatment and that the SIRIUS trial is representative of this comparison. Consequently, the ERG requested analyses based on the exacerbation rates and utilities recorded in SIRIUS, but the company claimed there was no time within the STA process to perform a full reanalysis and undertook a scenario analysis where utilities estimated from SGRQs gathered in SIRIUS were used while using the exacerbation rates from MENSA. The company did not report results for the GSK PP excl. stable mOCS claiming that there were too few patients in this sub-population in SIRIUS.

Table 66: Utilities measured in SIRIUS and used in the company's exploratory analysis

	Full Trial Population (ITT from SIRIUS)	GSK PP excl. stable mOCS	GSK PP
	Mean (SE)	Mean (SE)	Mean (SE)
Add-on mepolizumab: All patients	0.710 (0.027)	N/A	0.711 (0.028)
SoC	0.706 (0.026)	N/A	0.718 (0.029)
Add-on mepolizumab: Meeting CC	0.716 (0.029)	N/A	0.696 (0.036))

SoC: Standard of care; CC: continuation criteria

The ERG consider that the continuation criteria proposed by the company (i.e. continue on treatment unless the exacerbation rate increases) imply that a subgroup of patients could remain on treatment even when experiencing no improvement. The ERG requested that the company present exploratory analyses to assess the impact on the ICER of the amending the continuation criteria such that patients had to improve by a certain amount (as gauged by reduction of exacerbations or OCS use). The

company replied that it did "not believe it is appropriate" to quantify the level of improvement in terms of reduction of exacerbations because for patients "on maintenance OCS, who may be less likely to experience a further reduction in exacerbations", mepolizumab "provides the opportunity to reduce OCS exposure". However, in response to this request, the company reported results of exploratory analyses varying both the percentage of patients meeting the continuation criteria and the time to continuation assessment. The ERG noted that the validity of these exploratory analyses was limited since the exacerbation rates and percentage of patients meeting the continuation criteria did not appear to have been recalculated accordingly.

Finally, to assess the impact of the possible double-counting described by the company from assigning disutilities to exacerbations, the ERG requested that an analysis be performed excluding these disutilities.

The results of the analyses undertaken by the company following the clarification process are provided in

Table 67. The company did not perform any analyses exploring the effect on the ICER of changing the continuation rule such that only patients who had experienced a reduction in exacerbations continued treatment.

Table 67: Results for scenario analyses performed in response to clarification questions

	GSK PP excl. stable mOCS					GSK PP				
	Total cost (£)	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**	**Total cost (£)**	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**
Base case										
Mepo	[redacted]					[redacted]				
SoC	[redacted]				15,394	[redacted]				19,526
Asthma related mortality: Watson *et al.* / Roberts *et al.* (option 1)										
Mepo	[redacted]					[redacted]				
SoC	[redacted]				20,203	[redacted]				26,648
Asthma related mortality: Watson *et al.* / Roberts *et al.* (option 2)										
Mepo	[redacted]					[redacted]				
SoC	[redacted]				20,735	[redacted]				27,544
DREAM population (EQ-5D utilities)										
Mepo	[redacted]					[redacted]				

SoC	[redacted]				16,907	[redacted]				17,630
Meta-analysis of MENSA and DREAM (EQ-5D utilities)										
Mepo	[redacted]					[redacted]				
SoC	[redacted]				17,269	[redacted]				19,932
Meta-analysis of MENSA and DREAM (SGRQ-mapped utilities)										
Mepo	[redacted]					[redacted]				
SoC	[redacted]				14,679	[redacted]				18,779
Using the SGRQ-mapped utilities from SIRIUS (exacerbation rates from MENSA)										
Mepo	N/A		N/A			[redacted]				
SoC	N/A	N/A	N/A	N/A	N/A	[redacted]				32,374
No disutilities from exacerbations										
Mepo	[redacted]					[redacted]				
SoC	[redacted]				16,010	[redacted]				20,426

5.2.12 Model validation and face validity check

The company provided the following details with regards to model validation:

"Two advisory boards with respiratory clinicians and UK health economists were also undertaken … to test the clinical assumptions underpinning the model and approach to the modelling in general. Discussions which materially affected our approach included the model structure (exacerbations as a health state versus a transient event) as well as advice for deviating from the NICE Reference Case with regards to utilising SGRQ (from MENSA) derived utilities over EQ-5D collected in Phase IIb study DREAM. During the iterative process of the economic evaluation development, the model underwent interim QCs by the model developers (Pharmerit). Further the model also underwent two rounds of QC performed by an additional third party vendor (ICON). A QA was performed by a GSK analytics group and covered a critique of the following:

- *Completeness of model documentation and availability of the model (Excel/VBA application)*
- *General checklist of validity and credibility of the model*
- *Completeness and accuracy of reporting of model results"*

The ERG performed additional model validation checks when critiquing the company's submitted evidence. These validation checks included: white-box testing (detailed checking of inputs, code / formulae); black-box testing (changing inputs to see if outputs change as expected); testing face-

validity (comparing model results to expectations); and comparison of deterministic and probabilistic ICERs.

The main issues are summarised in Section 5.2.13.

5.2.13 Overview of the ERG's critique of the cost-effectiveness evidence

This section provides an overview of the issues previously discussed, concentrating on the main areas of uncertainty or disagreement.

Continuation criteria

The ERG considers that the continuation criteria proposed by the company (i.e. continue on treatment unless the exacerbation rate increases) implies that a subgroup of patients could remain on treatment even when experiencing no improvement. In their response to clarification questions, the company stated that "from clinical feedback it is clear that in practice patients will be assessed as part of their routine follow-up to ensure only those who continue to benefit from treatment remain on treatment." Therefore, the continuation criteria used in the model may not be aligned to clinical practice, particularly for those patients who not on mOCS.

Inclusion of the mOCS users with <4 exacerbations in the GSK PP

The ERG notes that the difference in the estimated ICERs per QALY gained between the GSK PP and the GSK PP excl. stable mOCS suggest that the use of mepolizumab in mOCS users with <4 exacerbations may have a high ICER. In response to the ERG's clarification questions, the company undertook a scenario analysis for this sub-population that resulted in an ICER of £78,716 per QALY gained (Table 64).

Exacerbation rates after continuation assessment

The exacerbation rates used in the model before continuation assessment were calculated by dividing the number of exacerbations by the number of person-years of exposure in MENSA. On the contrary, the exacerbation rates used for the rest of the treatment for patients on mepolizumab meeting the continuation criteria were calculated using a negative binomial model, based on the data of patients meeting the continuation criteria in MENSA from Week 16 to end of study (Week 32). The ERG note that this is not ideal for three reasons: (i) the future rates of asthma observed in patients who met the continuation criteria (which was a non-worsening of the exacerbation rate) are likely to be higher than the rates observed due to regression to the mean; (ii) the exacerbation rate is measured during a short period (16 weeks), which results in uncertainty, and; (iii) measurements may be subject to potential inaccuracy due to the seasonal nature of asthma exacerbations.

Asthma-related mortality

The company based its modelling of ARM using the following assumptions in the base case: ARM only happens following a clinically significant exacerbation; following a hospitalisation the rates of ARM are those reported by Watson *et al*.[1] which are supplemented by the relative rates of ARM outside of hospital reported in the NRAD report.[22]

Watson *et al*. used a constant rate of ARM for those aged 45 years and over, however data reported by Roberts *et al*.,[2] indicate that the rate of ARM is approximately six times higher in the 65 years and over group than that in the 45-54 years age group. The ARM rate for those aged 45 years and over in Watson *et al* is likely to overestimate mortality between the ages of 45 and 65 and underestimate it above the age of 65 years. Given that the base case analysis uses a median age of 50.1 years and a treatment duration of 10 years, the ERG believes that the rate of ARM is likely to be overestimated during the treatment period, therefore overestimating the benefits of mepolizumab.

Utility values

The company claimed that the EQ-5D suffered from a ceiling effect and poor sensitivity in severe asthma. Therefore, the company used an alternative instrument, the SGRQ, and mapped to the EQ-5D using an algorithm proposed by Starkie *et al*.[50] to predict EQ-5D utility from the SGRQ in subjects with COPD. The ERG notes that if the mapping algorithm correctly predicts EQ-5D scores of patients with severe asthma then the mapping performed would not address the claimed deficiencies of the EQ-5D in severe asthma.

In addition to HRQoL measurements for day-to-day symptoms, the company's model included utility decrements to account for exacerbations. The CS states: "SGRQ theoretically captures disutility associated with an exacerbation, since instrument items ask patients to retrospectively capture their HRQL (i.e. beyond the moment when the instrument is administered). However it does not explicitly capture the HRQL impact of an exacerbation event." The CS also claims that "this approach is no different than that utilised in the omalizumab NICE MTA".[11] The ERG noted that this assertion is not strictly accurate, given that a different HRQoL measuring instrument was used in the omalizumab NICE MTA, namely AQLQ.[60] Furthermore, the SGRQ includes questions about events happening in the last three months whereas AQLQ only asks about the last two weeks. The ERG notes that in the omalizumab MTA, "the Committee preferred the direct estimates of EQ-5D, in line with the NICE reference case" rather than mapped EQ-5D values.[11]

OCS sparing

The CS included a scenario analysis that took into account the costs and consequences of long-term systemic OCS usage. This analysis had several limitations: (i) it used OCS sparing data from the ITT population of SIRIUS instead of the company's proposed populations; (ii) it used OCS sparing data

from SIRIUS while assuming that reductions in the rates of exacerbation observed in MENSA were appropriate; (iii) the time horizon considered was 10 years instead of lifetime costs and utility decrement from fractures (resulting from osteoporosis) were not considered; (iv) some utility decrements estimated as chronic conditions were considered as one-off disutilities, and; (v) neither the proportion of the cohort that was alive at each cycle was considered to calculate the incidence of AEs nor the patients that suffered chronic disutilities from AEs that died were accounted for.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook a number of additional sensitivity analyses using the company's model. The results produced from key analyses undertaken by the ERG are reported in Section 6.

The ERG has concerns regarding the definition of the GSK PP. More precisely, the ERG believes that the blood eosinophil count of ≥150 cells/μL at screening does not seem to be a valid criterion to find a population in which mepolizumab is more effective in the medium- and long-term for two reasons. Firstly, clinical advisors to the ERG stated that 150 cells/μL is a relatively low threshold, well within the normal range. Secondly, as blood eosinophil counts fluctuate, the use of a value on a particular day may not be appropriate. Furthermore, all patients with a blood eosinophil count of ≥300 cells/μL in the previous year would have met the screening criteria if the screening had been undertaken on a day where the blood eosinophil count was high and therefore the results from these patients provide informative data.

The ERG would have preferred a base case analysis that was not restricted by the blood eosinophil count at screening but which still maintained a requirement for four or more exacerbations. However, the ERG did not have access to the necessary data and did not request these data or the corresponding analysis to be undertaken by the company as part of the clarification process. As such, the exploratory analyses presented in this section do not fully represent the true ERG base case.

The ERG modified some of the settings of the company's base case analysis for its analyses. The exploratory analyses include the following amendments:

1) Use of directly measured EQ-5D scores instead of the scores mapped from SGRQ (therefore adhering to the NICE Reference Case and the preference of the Appraisal Committee in the omalizumab MTA);
2) Use of asthma-related mortality rates estimated by the company combining the data from Watson *et al.*[1] and Roberts *et al.*[2] in response to the ERG's clarification questions (described as Option 2 in Section 5.2.11.4);
3) Based on feedback from the clinical experts to the ERG, assuming that a stopping rule of 10 years was inappropriate and that no fixed stopping rule would be applied;

4) Using the average length of the exacerbations measured in MENSA instead of the time over which EQ-5D was captured in Lloyd *et al*.;[51]
5) Setting the exacerbation rates for those meeting the continuation criteria to those observed in the COSMOS study. However, the ERG did not have access to the exacerbation rates for the GSK PP and GSK PP excl. stable mOCS in COSMOS. In order to overcome this limitation, the ERG estimated these rates based on the exacerbation rate measured in COSMOS in patients that had been on mepolizumab during MENSA, as reported in the company's clarification response (rate=0.90). The ERG estimated the rates for the GSK PP and GSK PP excl. stable mOCS by multiplying this rate by the RRs between rates of the ITT population and GSK PP and GSK PP excl. stable mOCS as used in the base case. The resulting rates are shown in Table 68.

Table 68: Exacerbation rates for patients on mepolizumab after continuation assessment based on COSMOS

	ITT		GSK PP excl. stable mOCS		GSK PP	
	Annual rate	4-weekly rate	Annual rate	4-weekly rate	Annual rate	4-weekly rate
Base case	0.550	0.042	0.723	0.056	0.645	0.050
COSMOS	0.900	0.069	1.183†	0.091	1.054‡	0.081

† 0.9*(0.723/0.550)
‡ 0.9*(0.645/0.550)

The ERG also reproduced the analysis in the stable mOCS subgroup, consisting of the patients in the GSK PP who are not within the GSK PP excl. stable mOCS. This analysis was based on the ERG base case but used the utilities (SGRQ-mapped), exacerbation rates, and percentage of patients meeting the continuation criteria observed in this subgroup. The exacerbation rate for patients meeting the continuation criteria was calculated following the same rationale as in the ERG's base case.

The ERG considers that the scenario analysis undertaken by the company using utilities measured in SIRIUS was insufficient because the exacerbation rates in SIRIUS were very different to those in MENSA. Accordingly, the ERG undertook an exploratory analysis using the exacerbation rates measured in SIRIUS for all three sub-populations. Unfortunately, the exacerbation rates for patients on mepolizumab who met the continuation criteria were not reported for SIRIUS. In order to estimate a lower bound for the ICER, the ERG made the optimistic assumption that the rates would be equal to those used in the ERG's base case. The ERG assumed that the percentage of patients meeting the continuation criteria was the same as in MENSA and included the OCS sparing benefits based on median OCS reduction. It was not possible to perform the analyses for the GSK PP excl. stable mOCS due to the small size of this population in SIRIUS. For these exploratory analyses, the utilities

measured in SIRIUS were used (see Table 66). The ERG noted that the utility values reported in SIRIUS for the GSK PP (whereby the utility of SoC was higher than that for all patients on mepolizumab, which in turn is higher than the utility for patients on mepolizumab who met the continuation criteria) were counterintuitive, probably due to the reduced size of this population. Considering the slight difference in this trial between the ITT population and the GSK PP (the blood eosinophil count of ≥150 cells/μL at screening threshold), the ERG decided to include an additional scenario where the utilities reported for the ITT population are also used for the GSK PP.

The ERG also performed exploratory analyses comparing mepolizumab with omalizumab and SoC incorporating the ERG's five preferred assumptions described above. The ERG undertook scenario analyses based on the following alternative assumptions:

A. Using the assumed annual cost of omalizumab reported in the omalizumab MTA. The company conducted a study to estimate the cost of the omalizumab treatment in clinical practice. The results of the study concluded that the cost of omalizumab was noticeably higher than that used in the omalizumab MTA, thereby implying that higher doses of omalizumab were being used. The ERG has no reason to dispute the values presented by the company but argues that it is unclear whether this change in the dosing has any impact on the effectiveness of omalizumab. Therefore, in order that the costs and efficacy data are derived from the same source, the assumed cost of omalizumab from the MTA were considered more appropriate.
B. Using the exacerbation RRs (compared with SoC) estimated from patients on mOCS in SIRIUS for patients on mepolizumab after continuation assessment. The NICE guidance recommends omalizumab for patients on "continuous or frequent treatment with oral corticosteroids"[11], which was equivalent to "maintenance OCS" during the appraisal. The ERG believes that omalizumab should be compared to mepolizumab in the population in which omalizumab is recommended. The company used the exacerbation RR of omalizumab for the ITT population (0.373) instead of the one reported for the maintenance OCS subgroup (0.293).[45] The ERG did not have access to the exacerbation RR for mepolizumab for patients on mOCS calculated from the MENSA trial, therefore the RR calculated in the GSK PP of the SIRIUS trial (0.77) was used instead of the value of 0.316 used in the company base case. The ERG comments that its preferred value for mepolizumab, is closer to the RR reported for patients on mOCS in the ITT population of the MENSA trial, these values were 0.8 for 100mg SC mepolizumab and 0.52 for 75mg IV mepolizumab.
C. Using a random effects model to calculate the exacerbation RR for patients before continuation assessment. Given the ERG's concerns regarding potential heterogeneity between omalizumab and mepolizumab trials, the ERG considered that a random effects

model (with a reference prior) would be more appropriate for the NMA than the fixed effects model used by the company.

Finally, the ERG undertook an exploratory analysis which combines all of these scenarios; this represents the ERG's base case. It should be noted that for the ERG's analyses which incorporate scenario numbers 1-5 (excluding scenario B) the calculated RR for mepolizumab is greater than in the CS due to the use of COSMOS data.

The results of all exploratory analyses undertaken by the ERG are presented in Section 6.

5.4 Conclusions of the cost effectiveness section

The CS was generally well written but was missing a few details. The model was conceptually sound and the implementation contained relatively few errors, which were mainly concentrated within the OCS sparing analyses.

The ERG has concerns regarding how the GSK PP has been defined which required a blood eosinophil count of ≥150 cells/μL at screening and it was unclear whether it was going to impact the effectiveness of mepolizumab in the medium- and long-term, especially seeing that a blood eosinophil count of ≥300 cells/μL in the previous year failed to have a significant impact.

The ERG notes that the comparator for mepolizumab should include mOCS, given that the GSK PP excl. stable mOCS group had suffered four or more exacerbations in the previous year, a sign of a poorly controlled asthma in Step 4, and that Step 5 treatment included the use of mOCS. The addition of mOCS in patients who are not contraindicated would likely reduce the average number of exacerbations and therefore reduce the benefit of mepolizumab. The SIRIUS trial could have given a better insight into this comparison, but the analysis using the data from SIRIUS contained a high degree of uncertainty due to the small size of the GSK PP in this trial.

For these reasons, the ERG considers that there remains uncertainty surrounding the true effectiveness of mepolizumab add-on treatment compared with standard of care.

The ERG preferred to change some of the assumptions from the company's base case analysis. It is worth noting that the ERG's base case comprised of a combination of scenarios which were individually considered in the exploratory analyses undertaken by the company and one extra scenario proposed by the ERG. Further, the ERG were not able to assess its preferred base case population, the ITT population with ≥4 exacerbations as the data were not available, although the ERG acknowledges these were not requested at the clarification stage.

6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG defined its own base case using alternative assumptions to those presented in the CS. First, the ERG undertook an exploratory analysis combining four different scenario analyses that were either presented in the CS or in response to the clarification process: the ERG believed these assumptions to be more plausible than those within the company's base case. Table 69 shows the deterministic results for the four scenario analyses separately and the results for a combined analysis using probabilistic sensitivity analyses using 2,000 iterations. For the sake of brevity, deterministic results were not presented although the ERG notes that there were only slight differences between estimates of the ICER produced by probabilistic and deterministic methods.

The ERG preferred to use the exacerbation rates for patients on mepolizumab after the continuation assessment from COSMOS rather than from MENSA. The deterministic results for the scenario analysis using these rates are also shown in Table 69. The ERG's base case combines the four scenario analyses with the use of rates from COSMOS. Table 69 demonstrates that the changes to the company's base case settings for the ERG's base case analysis have a large impact on the ICER, increasing it from £19,526 to £35,440 per QALY gained ([redacted] QALYs gained at a cost of [redacted]) in the GSK PP, from £15,394 to £33,520 ([redacted] QALYs gained at a cost of [redacted]) in the GSK PP excl. stable mOCS, and from £31,659 to £72,596 ([redacted] QALYs gained at a cost of [redacted]) in the ITT population.

The ERG considers that a more plausible ICER would be calculated using data from the ITT population with ≥4 exacerbations, rather than with an additional criterion of having ≥150 cells/μL at screening. However, the ERG did not have the required data to produce this analysis.

The cost-effectiveness acceptability curves for the GSK PP excl. stable mOCS and for the GSK PP based on the ERG's base case are provided in Figure 16 and Figure 17, respectively. Using the ERG's base case, the probability of add-on mepolizumab having a cost per QALY gained below a threshold of £30,000 was estimated to be 0.235 for the GSK PP excl. stable mOCS and 0.106 for the GSK PP. Using a threshold of £20,000 per QALY gained these values decrease to 0.00 for both populations.

Table 69: Results of the exploratory analyses undertaken by the ERG

Scenario Number		ITT population					GSK PP excl. stable mOCS					GSK PP				
		Total cost (£)	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (£)**	**Total cost (£)**	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (£)**	**Total cost (£)**	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (£)**
	Company's base case (probabilistic)															
	Mepo	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	31,692	[redacted]	[redacted]	[redacted]	[redacted]	15,478	[redacted]	[redacted]	[redacted]	[redacted]	19,511
1	Source of health state utilities: EQ-5D (DREAM)															
	Mepo	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	40,392	[redacted]	[redacted]	[redacted]	[redacted]	18,429	[redacted]	[redacted]	[redacted]	[redacted]	20,863
2	Asthma-related mortality: Watson *et al.* / Roberts *et al.* (company option 2)															
	Mepo	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	42,728	[redacted]	[redacted]	[redacted]	[redacted]	20,735	[redacted]	[redacted]	[redacted]	[redacted]	27,544
3	Biologic treatment duration: Life time															
	Mepo	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	32,130	[redacted]	[redacted]	[redacted]	[redacted]	15,571	[redacted]	[redacted]	[redacted]	[redacted]	19,763
4	Source of duration of utility decrement for an exacerbation: MENSA															
	Mepo	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	32,480	[redacted]	[redacted]	[redacted]	[redacted]	15,690	[redacted]	[redacted]	[redacted]	[redacted]	19,963
5	Exacerbation rates for patients meeting the CC based in COSMOS															
	Mepo	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	37,190	[redacted]	[redacted]	[redacted]	[redacted]	17,240	[redacted]	[redacted]	[redacted]	[redacted]	22,239

	Combination of company's scenario analyses 1-4 (probabilistic)															
	Mepo	[redacted]														
	SoC	[redacted]				59,094					28,184					30,410
	ERG's base case 1-5 (probabilistic)															
	Mepo	[redacted]														
	SoC	[redacted]				72,596					33,520					35,440

CC = continuation criteria; N/A = not available

Figure 16: Cost-effectiveness acceptability curve for the GSK PP excl. stable mOCS (ERG's base case)

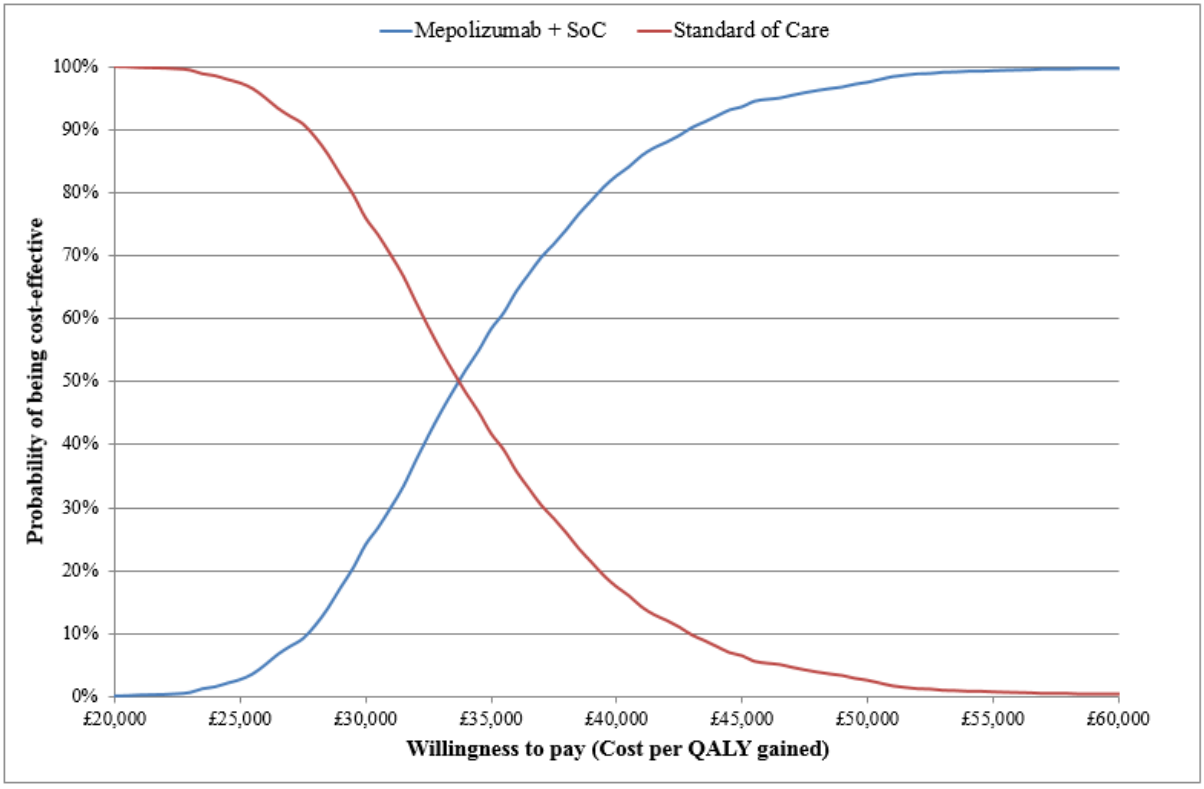
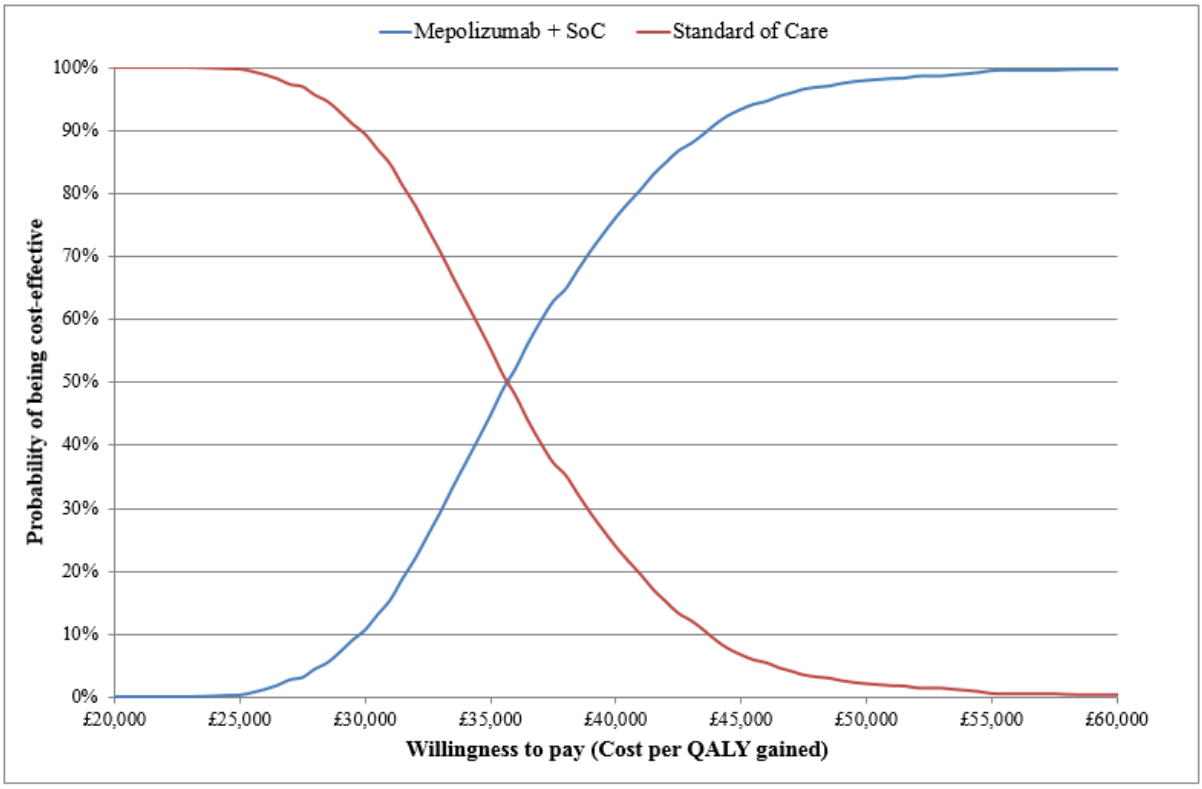


Figure 17: Cost-effectiveness acceptability curve for the GSK PP (ERG's base case)



Whilst the ERG has presented their estimates of the most plausible ICER, it is possible that the Appraisal Committee may wish to only apply some of the changes made by the ERG. As such, Table 70 shows the ICERs for all the possible permutations of applying (or not) the five assumptions that differ from the base case of the company and the ERG. The first row of results in Table 70 contains those produced by the company's base case, whilst the final row of results represents the ERG base case. From Table 70, it is noticeable that there is interaction between the scenarios. For example, individually the first and second scenarios (relating to the source of health state utilities and the assumed mortality rate following hospitalisation) change the ICER to £18,429 and £20,735 respectively for the GSK population excl. stable mOCS from a deterministic value of £15,394; however, when the two are combined the ICER increases to a value of £29,993.

Table 70: Results from different permutations of scenario analyses performed by the ERG

Scenario Number										
1	2	3	4	5	GSK PP excl. stable mOCS			GSK PP		
					Δ Costs (£)	Δ QALYs	ICER (£)	Δ Costs (£)	Δ QALYs	ICER (£)
					[redacted]	[redacted]	15,394	[redacted]	[redacted]	19,526
				✓	[redacted]	[redacted]	17,240	[redacted]	[redacted]	22,239
			✓		[redacted]	[redacted]	15,690	[redacted]	[redacted]	19,963
			✓	✓	[redacted]	[redacted]	17,550	[redacted]	[redacted]	22,704
		✓			[redacted]	[redacted]	15,571	[redacted]	[redacted]	19,763
		✓		✓	[redacted]	[redacted]	17,480	[redacted]	[redacted]	22,565
		✓	✓		[redacted]	[redacted]	15,885	[redacted]	[redacted]	20,226
		✓	✓	✓	[redacted]	[redacted]	17,807	[redacted]	[redacted]	23,057
	✓				[redacted]	[redacted]	20,735	[redacted]	[redacted]	27,544
	✓			✓	[redacted]	[redacted]	22,864	[redacted]	[redacted]	30,798
	✓		✓		[redacted]	[redacted]	21,496	[redacted]	[redacted]	28,686
	✓		✓	✓	[redacted]	[redacted]	23,628	[redacted]	[redacted]	31,963
	✓	✓			[redacted]	[redacted]	19,463	[redacted]	[redacted]	25,435
	✓	✓		✓	[redacted]	[redacted]	21,712	[redacted]	[redacted]	28,818
	✓	✓	✓		[redacted]	[redacted]	20,105	[redacted]	[redacted]	26,378
	✓	✓	✓	✓	[redacted]	[redacted]	22,371	[redacted]	[redacted]	29,803
✓					[redacted]	[redacted]	18,429	[redacted]	[redacted]	20,863
✓				✓	[redacted]	[redacted]	21,620	[redacted]	[redacted]	24,346
✓			✓		[redacted]	[redacted]	18,856	[redacted]	[redacted]	21,362
✓			✓	✓	[redacted]	[redacted]	22,111	[redacted]	[redacted]	24,905
✓		✓			[redacted]	[redacted]	18,793	[redacted]	[redacted]	21,218
✓		✓		✓	[redacted]	[redacted]	22,140	[redacted]	[redacted]	24,848
✓		✓	✓		[redacted]	[redacted]	19,253	[redacted]	[redacted]	21,753
✓		✓	✓	✓	[redacted]	[redacted]	22,668	[redacted]	[redacted]	25,446
✓	✓				[redacted]	[redacted]	29,993	[redacted]	[redacted]	32,285
✓	✓			✓	[redacted]	[redacted]	35,156	[redacted]	[redacted]	37,225
✓	✓		✓		[redacted]	[redacted]	31,612	[redacted]	[redacted]	33,865
✓	✓		✓	✓	[redacted]	[redacted]	36,996	[redacted]	[redacted]	38,941
✓	✓	✓			[redacted]	[redacted]	26,920	[redacted]	[redacted]	29,163
✓	✓	✓		✓	[redacted]	[redacted]	32,006	[redacted]	[redacted]	34,121
✓	✓	✓	✓		[redacted]	[redacted]	28,165	[redacted]	[redacted]	30,411
✓	✓	✓	✓	✓	[redacted]	[redacted]	33,460	[redacted]	[redacted]	35,510

The ERG noted that the GSK PP included a subgroup (the stable mOCS) for which the company estimated an ICER of £78,716 per QALY gained. An exploratory analysis was conducted by the ERG that amended the company's estimate by using scenario numbers 2-5 in Table 69. The utility estimate was held at the values reported by the company even though these were mapped from SGRQ values, because direct EQ-5D values were not available for this sub-population. This resulted in an ICER for the stable mOCS population of £167,778 per QALY (see Table 71).

Table 71: Results for the stable mOCS population based on the ERG's base case analysis

	Total Cost (£)	**Δ Cost (£)**	**Total QALY**	**Δ QALY**	**ICER (£)**
Mepolizumab + standard of care	[redacted]		[redacted]		
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	167,778

The ERG performed exploratory analyses using data collected in the SIRIUS trial combined with scenario numbers 2-5 in Table 69. The utility estimates was held at the values reported by the company even though these were mapped from SGRQ values; this was because direct EQ-5D values were not available for this sub-population. The company reported population-specific utilities that were mapped from SGRQ values, but these appeared counterintuitive as SoC have a higher utility value than patients on mepolizumab and the utility for all patients on mepolizumab was higher than for patients meeting the continuation criteria (Table 66). These exploratory resulted in the ICERs shown in

Table 72. Both ICERs were greater than £75,000 per QALY gained. The GSK PP results are subject to considerable uncertainty due to a small patient population; the population in SIRIUS who would be categorised in the GSK PP excl. stable mOCS group were too small for meaningful analyses to be undertaken.

These results imply that at least [redacted] extra QALYs would have to be gained from OCS sparing for the ICER to be under £30,000 for QALY gained. The corresponding number of additional QALYs required to have an ICER under £20,000 per QALY gained was [redacted].

Table 72: Result of the exploratory analyses based on SIRIUS*

	ITT					GSK PP				
	Total cost (£)	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (£)**	**Total cost (£)**	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (£)**
ERG's base case + utilities and exacerbation rates from SIRIUS (population-specific utilities)										
Mepo	[redacted]					[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	84,700	[redacted]	[redacted]	[redacted]	[redacted]	147,637
ERG's base case + utilities and exacerbation rates from SIRIUS (using ITT utilities)										
Mepo	[redacted]					[redacted]				
SoC	[redacted]	[redacted]	[redacted]	[redacted]	84,700	[redacted]	[redacted]	[redacted]	[redacted]	79,804

*All patients in the SIRIUS trial were dependent on maintenance OCS

The ERG undertook analyses comparing mepolizumab add-on to omalizumab add-on in those patients on mOCS (

Table 73). The ERG explored the impact of alternative assumptions regarding the list price of omalizumab (using the one reported in the omalizumab MTA rather than that reported in the CS) and the use of exacerbation RRs applicable to the mOCS population rather than the ITT population (given that NICE issued a recommendation to treat with omalizumab only patients who were on maintenance OCS). The ERG also preferred the use of the random effects model for the NMA rather than the fixed effects model. Finally, the ERG combined these three alternative assumptions. This represented the ERG's base case and resulted in an ICER for omalizumab compared with mepolizumab of £43,084. It is worth noting that these analyses were performed using the PAS price of mepolizumab and the list price of omalizumab. The ERG repeated these same analyses using the PAS price for both mepolizumab and omalizumab and presented these results in a confidential appendix.

Table 73: Results of exploratory analyses ERG omalizumab

Scenario Number		Mepo	Omalizumab	Mepo vs. omalizumab	SoC	Mepo vs. SoC
	Deterministic results incorporating scenario numbers 1-5 from Table 69					
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER			**Dominant**		**£73,573**
	Probabilistic results incorporating scenario numbers 1-5 from Table 69					
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER			**Dominant**		**£73,369**
A	Source of annual omalizumab cost: omalizumab MTA (probabilistic)					
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER			**Dominant**		**£72,965**
B	Using RRs for mOCS (probabilistic)					
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER			**£338,590***		**£104,129**
C	Random effects model for the NMA (probabilistic)					
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER			**Dominant**		**£73,855**
	Combination of scenario numbers A-C (probabilistic): ERG base case					
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER			**£43,084***		**£105,140**

*These ICERs lie in the South West quadrant and imply the costs saved per QALY lost with mepolizumab

The results of the analyses suggest that the cost of omalizumab is a key parameter in determining the estimated cost difference between mepolizumab and omalizumab.

The assumed RRs applied for mepolizumab and omalizumab had a large impact on the estimated clinical effectiveness: with the values used by the company mepolizumab produces an additional [redacted] QALYs compared with omalizumab; using the values proposed by the ERG omalizumab becomes the more clinically effective option, producing [redacted] QALYs compared with mepolizumab, but at an extra cost of [redacted].

7 End of life

NICE end of life supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;
- The treatment is licensed or otherwise indicated, for small patient populations.

The ERG notes that the company did not make a case for mepolizumab to be considered under the end of life criteria. The ERG does not believe that mepolizumab meets the criteria.

8 Overall conclusions

The submitted evidence is consistent with the NICE scope for interventions, comparators and relevant outcomes. The population in the scope is *"adults with severe eosinophilic asthma"* but there are difficulties in specifying the degree of severity and eosinophilia. The CS provides data on the ITT populations plus two "GSK proposed populations" based on exacerbation history, eosinophil count and use of mOCS. The ERG considers that the *post hoc* analyses used to justify the GSK populations should be interpreted with caution, particularly the blood eosinophil cut-off of ≥150 cells/μL at screening. The criterion of ≥4 exacerbations in the previous year appears more clinically robust.

The NMA of mepolizumab vs. omalizumab appeared methodologically robust but the results should be interpreted with caution, given the heterogeneity between trials and the fact that only a subset of trial patients were eligible for both mepolizumab and omalizumab.

In the comparison of mepolizumab with SoC three assumptions were shown to markedly affect the ICER: whether to use direct EQ-5D data or SGRQ data mapped to the EQ-5D; whether the mortality rates following hospitalisation were constant after the age of 45 years or whether the rate would increase in older patients; and the assumed number of asthma exacerbations beyond year one for those who continue on mepolizumab.

The ERG comments that a more plausible ICER would be one calculated using data from the ITT population with ≥4 exacerbations, rather than with an additional criterion of having ≥150 cells/μL at screening. However, the ERG did not have the required data to estimate this value.

In the comparison of mepolizumab with omalizumab two assumptions were observed to markedly affect the ICER these were: the assumed cost of omalizumab; and the RR assumed for mepolizumab in patients on mOCS.

8.1 Implications for research

Further data on the relationship between blood eosinophil level and clinical outcomes would be useful. Long-term data on AEs and effects of anti-mepolizumab antibodies would be valuable. Head-to-head comparison of mepolizumab and omalizumab in the population eligible for both drugs would also be useful. Further data on the utility of patients with severe asthma would improve the accuracy of the cost-effectiveness results.

Further data on the long-term AEs of mOCS, plus the health-related utility decrements and costs associated with these, would be valuable.

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Mepolizumab for treating severe eosinophilic asthma: A Single Technology Appraisal

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For exacerbations requiring hospitalisation, RRs for mepolizumab (100mg SC and 75mg IV groups combined) vs. placebo, meta-analysed across MENSA and DREAM, were: RR=0.50 (95% CI 0.28, 0.89) in the ITT population; RR=0.44 (95% CI 0.19, 1.02) in the GSK PP; RR=0.43 (95% CI 0.16, 1.12) in the GSK PP excl. stable mOCS; and RR=0.53 (95% CI 0.10, 2.75) in the stable mOCS population. In SIRIUS, hospitalisation numbers were low (ITT: 7 for placebo vs. 0 for mepolizumab). Exacerbations requiring hospitalisation or ED visits showed a similar pattern. In terms of quality of life, differences on the St. George's Respiratory Questionnaire (SGRQ) for MENSA and SIRIUS for mepolizumab vs. placebo ranged from 5.0 to 12.8 units ($p<0.001$ for meta-analysed results), in all sub-populations except in stable mOCS patients where the difference ranged from 1.2 to 5.8 ($p=0.106$). The minimal clinically important difference [MCID] is 4 units. Differences on the Asthma Control Questionnaire (ACQ) meta-analysed across trials ranged from -0.34 to -0.78 ($p<0.001$ for all) across all sub-populations except in stable mOCS patients where the difference was ranged from 0.30 ($p=0.144$) to 0.43 ($p=0.007$) (MCID 0.5 units).

Steroid reduction: The SIRIUS trial had a primary endpoint of percentage reduction in OCS dose whilst maintaining asthma control. Odds ratios (OR) for mepolizumab vs. placebo were: OR=2.39 (95% CI 1.25, 4.56) for ITT; OR=1.81 (95% CI 0.86, 3.79) for GSK PP; OR=2.75 (95% CI 0.72, 10.59) for GSK PP excl. stable mOCS. Absolute differences between mepolizumab and placebo for the proportion achieving a reduction in OCS dose whilst maintaining asthma control were 20% in the ITT population, 13% in the GSK PP, and 26% in the GSK PP excl. stable mOCS.

In terms of secondary outcomes in the GSK PP, the OCS dose was reduced by at least 50% in 48% of patients (mepolizumab) vs. 38% (placebo), giving an OR of 1.60 (95% CI 0.70, 3.64) and an absolute difference of 10%. A reduction in OCS dose to ≤5 mg was observed in 50% of patients (mepolizumab) vs. 40% (placebo), with an OR of 1.64 (95% CI 0.68, 3.93) and an absolute difference of 10%. In addition, OCS use was stopped completely in 13% (mepolizumab) vs. 8% (placebo), with an OR of 1.35 (95% CI 0.32, 5.78) and an absolute difference of 5%. Results were not significant in the GSK PP ($p>0.1$), though numbers were small. ORs and absolute differences were slightly more favourable in the ITT population than the GSK PP, and were generally statistically significant in the ITT population. Results in the GSK PP excl. stable mOCS were slightly more favourable than in the GSK PP but did not reach statistical significance, though numbers were small.

Subgroup analyses: *Post hoc* subgroup analyses and modelling were used to identify the two GSK proposed populations. The CS compares two options for eosinophil threshold: ≥150/μL at screening or ≥300/μL in the previous 12 months. Patients with ≥150/μL at screening had a greater reduction in exacerbations for mepolizumab vs. placebo than patients with <150/μL; this was not the case when the population was subgrouped using a threshold of ≥300/μL in the previous 12 months. The company

Clinical validity of sub-populations: The CS states that the thresholds for eosinophil level and previous exacerbations were clinically plausible and practical to implement according to severe asthma specialists. In terms of eosinophil level, the European Medicines Agency (EMA) concluded that eosinophil levels were not sufficiently predictive to justify a specific cut-off within their marketing authorisation. Clinical advisors to the ERG advised that a threshold of ≥300 cells/μL in the previous 12 months would be more appropriate for the diagnosis of eosinophilic asthma than ≥150/μL at screening, firstly because 150/μL is within the normal range and secondly because eosinophil levels can fluctuate. Clinical advisors to the ERG considered that a threshold of ≥4 previous exacerbations was clinically appropriate, and was consistent with NICE guidance for omalizumab which restricts the use of the drug to people requiring continuous or frequent treatment with oral corticosteroids (≥4 courses in the previous year).

Evaluation of the indirect comparison: The indirect comparison methods appear broadly appropriate. However, the ERG considers that the results of the random effects model provide a more appropriate (and more conservative) estimate than those of the fixed effects model given the heterogeneity between trials. The company also acknowledges that the results should be treated with caution since only a small proportion of patients in the mepolizumab and omalizumab trials were eligible for both treatments, and study populations differed in terms of severity.

1.4 Summary of cost effectiveness evidence submitted by the manufacturer

The manufacturer supplied a *de novo* cohort Markov model constructed in Microsoft Excel©. The perspective used was that of the NHS in England. The cycle length was set to four weeks and a lifetime time horizon (approximately 92 years) was used. A discount rate of 3.5% per annum was used both for costs and utilities. The model includes four states: (i) on-treatment before continuation assessment; (ii) on-treatment after continuation assessment; (iii) off-treatment and; (iv) death. All patients on a biologic treatment enter the model in the 'on-treatment before continuation assessment' state, until the continuation assessment. After continuation assessment, patients transition either to 'on-treatment after continuation assessment' or 'off-treatment' depending on whether or not they meet a continuation criteria: patients on mepolizumab continued on treatment unless the exacerbation rate worsened compared with the previous year whilst patients on omalizumab continued only if they achieved a physician-rated global evaluation of treatment effectiveness score of good or excellent. Patients in the 'on-treatment after continuation assessment' state transition to the 'off-treatment' state when they discontinue treatment. All patients on SoC enter the model in the 'off-treatment' state. During any cycle, patients can transition from any of the alive states to death as a consequence of either asthma-related mortality following an exacerbation or due to other causes.

mepolizumab compared with a group where mOCs had not been added. The SIRIUS trial could have provided an insight for mepolizumab in this comparison, but the analysis using the data from SIRIUS was subject to a high degree of uncertainty due to the small size of the GSK PP in this trial.

The ERG has concerns regarding the continuation criteria defined for mepolizumab. Grammatically this should be a continuation criterion but we have used continuation criteria to be consistent with the CS. According to these, all patients who did not experience a worsening in exacerbation rates would to receive mepolizumab. This implies that a proportion of patients would remain on mepolizumab despite experiencing This implies that a proportion of patients would remain on mepolizumab despite experiencing no numerical improvement in exacerbations, however patients could be receiving benefit in the form of reduced OCS exposure or symptomatic improvement. The ERG also has concerns regarding the calculation of exacerbation rates for patients meeting the continuation criteria: these rates were measured in the MENSA trial shortly after the beginning of treatment, based on a 16-week time span and therefore might not be representative of the long-term effectiveness of mepolizumab and may be affected by seasonality. Furthermore, there may be a regression to the mean.

Regarding the comparison with omalizumab, the ERG notes the importance of the decision taken by the company to use the cost of omalizumab as calculated through a study; this results in an estimated drug cost which was more than 40% higher than that reported within the assessment report of the omalizumab MTA.

For these reasons, the ERG believes that there is considerable uncertainty regarding the true cost-effectiveness of mepolizumab add-on treatment compared to standard of care and omalizumab.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

Clinical trial data were presented for the ITT population and the GSK proposed populations across a range of relevant clinical outcomes. Data were meta-analysed across trials. Whilst there were gaps in the data provided in the CS, more complete data were provided in the clarification response.

The model used appears conceptually appropriate with only a few minor implementation errors. It contained the functionality to assess the impact of changing parameters and relevant structural uncertainties on the ICER. A number of built-in alternative scenarios were included.

1.6.2 Weaknesses and areas of uncertainty

The ERG considers that the *post hoc* analyses used to justify the GSK proposed populations should be interpreted with caution, particularly the eosinophil threshold of ≥150 cells/μL at screening. The

results of the NMA should also be interpreted with caution, given the heterogeneity between the trials and the fact that only a subset of the trial patients was eligible for both mepolizumab and omalizumab.

The cost-effectiveness results are sensitive to the utility values used in the model and the methods used to model asthma-related mortality. Alternative methods of calculating exacerbation rates for patients meeting the continuation criteria also have a major impact on the ICER.

Both the company and clinicians consulted by the ERG claim a high disutility caused by the side effects of long-term use of OCS, however the scenario analysis undertaken by the company estimates only a very small benefit. The CS states that 'An OCS dose reduction and discontinuation approach were explored but the scenario analyses did not generate the expected upside of sparing patients from OCS.' GSK further states that the results presented in the CS 'are in contrast to those from the approach taken in the NICE omalizumab MTA which showed an improvement [in the ICER] by £4,000-£6,000/QALY gained and £10,000 - £17,000 /QALY gained'. Thus, the true benefits of OCS sparing appear uncertain. However, it is noted that the cessation of OCS use seemed to be greater for omalizumab than for mepolizumab, as described in section 5.2.11.3.

The key uncertainty in the clinical evidence base for mepolizumab versus omalizumab concerns the absence of head-to-head RCTs comparing these drugs. A key uncertainty in the cost-effectiveness modelling is the cost of the omalizumab treatment, which depends on the weight and IgE levels of a patient, and the estimate for the cost of omalizumab used in the company's model is markedly higher than that used in the previous NICE appraisal of omalizumab. In addition, some of the scenario analyses exploring the comparison between omalizumab and mepolizumab resulted in ICERs substantially different to that of the base case.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The probabilistic base case ICERs presented in the CS comparing mepolizumab with SoC were £19,511 and £15,478 per QALY gained for the GSK PP and GSK PP excl. mOCS, respectively. The ERG made five changes to the company's base case. These included: (i) using directly measured EQ-5D scores instead of the scores mapped from SGRQ; (ii) using the asthma-related mortality rates estimated by the company combining the data from Watson *et al.*[1] and Roberts *et al.*[2]; (iii) removing the use of a fixed duration stopping rule for mepolizumab treatment; (iv) calculating the QALY loss due to exacerbations using the average duration of exacerbations observed in MENSA and; (v) setting the exacerbation rates for those meeting the continuation criteria equal to those derived from the COSMOS study. When taken in isolation, each of these changes led to an increase in the ICER, the largest of which was attributable to the modelling of asthma-related mortality. The combined effect of these changes increases the probabilistic ICER from £19,511 per QALY gained to £35,440 per QALY

gained ([redacted] QALYs gained at a cost of [redacted]) in the GSK PP, and from £15,478 per QALY gained to £33,520 per QALY gained ([redacted] QALYs gained at a cost of [redacted]) in the GSK PP excl. stable mOCS. The ERG notes that using data from the ITT population with ≥4 exacerbations, rather than with an additional criterion of having ≥150 cells/μL at screening, would produce, in the opinion of the ERG, a more plausible ICER for mepolizumab versus SoC. However, the ERG did not have the data required to undertake this analysis.

For the comparison of mepolizumab versus omalizumab, the base case analysis presented in the CS, which does not incorporate the omalizumab PAS, concludes that mepolizumab dominates omalizumab. The ERG applied three alternative assumptions: (i) the cost of omalizumab (without the PAS) was based on that used within the previous NICE appraisal of omalizumab; (ii) the exacerbation RRs were based on a mOCS population, and; (iii) a random effects NMA model was applied. On the basis of this exploratory analysis, the ICER for omalizumab versus mepolizumab was approximately £43,000 per QALY gained. An estimate of the cost-effectiveness of mepolizumab compared to omalizumab when the omalizumab PAS is assumed is provided in a confidential appendix.

assessment for adherence to therapy before being termed refractory. The criteria relating to compliance was emphasised in the National Institute for Health and Care Excellence (NICE) guidance for omalizumab.[11] The CS assumes that all patients have been diagnosed as severe refractory eosinophilic asthmatic and are optimized on SoC before being considered eligible for add-on mepolizumab therapy.

Severe eosinophilic asthma: Eosinophilic asthma is a distinct phenotype of asthma characterised by tissue and sputum eosinophilia, a thickening of the basement membrane and, often, responsiveness to corticosteroids.[8] It can be present in mild, moderate or severe asthma.[8] It is, however, associated with more severe disease, late onset, atopy and steroid refractoriness. The diagnosis of eosinophilic asthma is problematic in clinical practice. Induced sputum eosinophil levels of 1-3%[8] are commonly interpreted as indicating eosinophilic disease, however, this test is impracticable in routine care. Alternatives include peripheral blood eosinophil counts, fractional exhaled nitric oxide (FeNO), serum immunoglobulin E (IgE), and periostin levels. However, a recent US review[8] reported that these have limited diagnostic accuracy: levels of blood eosinophils >300 cells/μL had a positive predictive value of only 50% in identifying an eosinophilic asthma phenotype (defined as sputum eosinophils of >2%), serum IgE had no correlation with eosinophilia,[12] studies relating to FeNO appeared inconsistent,[13-15] and the diagnostic utility of periostin was promising but is as yet undetermined. Further, a systematic review and meta-analysis of tests for eosinophilia found sensitivities and specificities of 0·66 (95% Confidence Interval (CI) 0·57–0·75) and 0·76 (95% CI 0·65–0·85) for FeNO; 0·71 (95% CI 0·65–0·76) and 0·77 (95% CI 0·70–0·83) for blood eosinophils; and 0·64 (95% CI 0·42–0·81) and 0·71 (95% CI 0·42–0·89) for IgE respectively.[16] One study concluded that thresholds for interpreting blood eosinophils varied greatly.[17] A Dutch study reported blood eosinophil cut-offs from a derivation and validation cohort, and concluded that the best diagnostic accuracy (for identifying sputum eosinophils >3%) was achievable at values of approximately 220 cells/μL for the derivation cohort, though diagnostic accuracy was reduced in the validation cohort.[18]

Despite only moderate diagnostic accuracy being reported for blood eosinophils in the literature, the test is used in clinical practice to monitor disease.[4] There is no national or international consensus on how to interpret such tests; however, clinical advisors to the ERG stated that a level of ≥300 cells/μL in the previous 12 months is a commonly used cut-off. The CS states *"Eosinophilic asthma inflammation can be measured in both blood and sputum, but recent studies have confirmed that late-onset severe refractory eosinophilic asthma can be reliably characterised by establishing blood eosinophil thresholds in the presence of high-dose ICS in a poorly controlled exacerbating phenotype"* (p 25-26), and references two articles[19, 20] to support this statement, both of which are re-analyses of the phase IIb trial, "Dose Ranging Efficacy And safety with Mepolizumab in severe asthma" (DREAM), which forms part of this submission. The ERG concludes that the use of blood

scope. The CS therefore provides data for the ITT trial populations and also for sub-populations of patients meeting higher thresholds for severity and eosinophil count (Section 3.1.3).

The three pivotal trials are as follows: DREAM (Pavord *et al*., 2012[19]), "Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma" (MENSA, Ortega *et al*., 2014[24]) and "Steroid Reduction with Mepolizumab Study" (SIRIUS, Bel *et al*., 2014[25]). The pivotal trials include patients requiring high-dose ICS plus additional controllers, with or without maintenance oral corticosteroids (mOCS) (DREAM and MENSA) or requiring mOCS (SIRIUS), and as such include severe asthma patients. SIRIUS includes patients on mOCS, which represents a more severe spectrum of patients than DREAM and MENSA. Two of the trials (DREAM and MENSA) also use a criterion of ≥2 asthma exacerbations requiring treatment with systemic corticosteroids in the previous 12 months, which has been accepted as a measure of loss of control by the international consensus statement from the Innovative Medicine Initiative (Bel et al. 2011). All patients were assessed for compliance and patients with clinically significant concurrent medical conditions were excluded from the trials. The criterion of ≥2 exacerbations in the previous year is not mentioned for SIRIUS, as the aim of the study was to assess mepolizumab's ability to reduce mOCS dose, and thus the associated side effect burden, independent of exacerbation baseline frequency, which may be reduced in patients on mOCS.

Forced expiratory volume in 1 second (FEV_1) <80% was a selection criterion for all three mepolizumab trials. However, the clinical advisors to the ERG noted that patients can have multiple exacerbations whilst having an FEV_1 of 80% or greater. As such, patients with FEV_1>80% are missing from the clinical evidence submitted by the company.

Eosinophilic asthmatics are usually defined as those with sputum eosinophils greater than 1-3%,[8] though as this test is difficult to perform in routine practice and is often not used. There is a lack of agreement about what surrogate markers can be used in clinical practice, and at what cut-off patients should be considered to be eosinophilic (see Section 2.1). The licence does not specify an eosinophil cut-off. The trials included in the CS have identified eosinophilic patients using various methods. MENSA and SIRIUS included patients with either blood eosinophils ≥150 cells/μL at screening or eosinophils ≥300 cells/μL in the past 12 months, whilst the earlier DREAM trial included patients with any of four criteria (blood eosinophils ≥300 cells/μL *or* sputum eosinophils ≥3% *or* exhaled nitric oxide (FeNO) ≥50 ppb *or* prompt deterioration of asthma control following ≤25% reduction in inhaled or oral corticosteroid dose in previous 12 months). The company provided data for the ITT population as well as for a more severe population based on eosinophil count and history of exacerbations (see below).

The company's rationale for the GSK PP is based on a set of *post hoc* modelling analyses and subgroup analyses of DREAM and MENSA, described further in Section 4.2.4.2. Briefly, subgroup analyses of both DREAM and MENSA showed that the reduction in exacerbations for mepolizumab vs. placebo was greater for patients with higher baseline blood eosinophils than for those with lower baseline eosinophils. In addition, the reduction in exacerbations was greater for patients with more previous exacerbations than those with fewer previous exacerbations in DREAM and MENSA. In addition, the company proposes that mOCS users meeting the eosinophil cut-off should be included in this population (even if they had fewer than 4 exacerbations in the past year) since mOCS users are likely to be a severe group and there are documented clinical benefits associated with reducing the use of mOCS.

The company's rationale for also presenting data for the "GSK PP excl. stable mOCS" population is that this population (excluding mOCS users with <4 previous exacerbations) may show greater effectiveness and cost-effectiveness, since the use of corticosteroids may already have reduced exacerbations in mOCS users, therefore there may be less potential to demonstrate a further reduction in exacerbations in these patients. The CS states that the primary objective in mOCS users would be to reduce steroid exposure whilst maintaining asthma control, but that it is challenging to fully capture the benefits of reducing steroid exposure in the clinical and cost-effectiveness analysis.

Clinical validity and feasibility of GSK PP: The CS (p80) states that, based on modelling and subgroup analyses, patients with ≥150 cells/µl baseline blood eosinophils at screening and ≥4 exacerbations in the 12 months prior to screening experienced the most benefit from therapy with add-on mepolizumab, and that *"the clinical viability of this conclusion was supported by independent severe asthma specialists' interpretation of the results."* The CS also states that *"clinical experts agree that this population is plausible and practical to implement in practice"* (CS p12). The statistical validity of the modelling and subgroup analyses is discussed in Section 4.2.4.2.

In terms of previous exacerbations, clinical advisors to the ERG considered that a threshold of ≥4 previous exacerbations was clinically appropriate. The CS also notes (p81) that the GSK PP is consistent with current NICE guidance for omalizumab which restricts use to people requiring continuous or frequent treatment with oral corticosteroids (≥4 courses in the previous year). Previous exacerbations (in the GSK PP and the subgroup analyses) are defined as exacerbations requiring systemic corticosteroids (or for subjects on mOCS, a two-fold or greater dose increase) and/or hospitalisations or ED visits. This is contrary to the definition supplied in the company's clarification response, but is the definition provided in the Fact Check process. Although predictive modelling reported in the CS appears to show a correlation between previous exacerbations and reductions in

In DREAM and MENSA, for the primary endpoint of exacerbations, for patients who withdrew, all data up to the time of patient withdrawal were included in the analyses. However, there are missing data for the period following withdrawal. The primary analysis made a standard assumption known as the Missing At Random (MAR) assumption. This assumes that future exacerbations for those who withdraw can be predicted from their exacerbation history prior to withdrawal and from the exacerbation rate of similar patients on the same treatment. Two sensitivity analyses were performed in which it was assumed that future exacerbations for patients who withdrew from a mepolizumab arm could be predicted based on the exacerbation rate in the placebo arm, not on the mepolizumab arm. Both analyses showed similar results to the primary analysis. The ERG is satisfied that the potential impact of missing data following withdrawal on the results of the analyses has been considered appropriately.

In SIRIUS, the primary efficacy endpoint was the percentage reduction in OCS dose during weeks 20-24 compared to the baseline dose, whilst maintaining asthma control. This was categorised as follows: 90% to 100% reduction; 75% to <90% reduction; 50% to <75% reduction; >0% to <50% reduction; or no reduction, lack of asthma control, or withdrawal from treatment. This was analysed using a proportional odds model for the above categories of oral steroid reduction, with covariates of region, number of years on oral steroids (<5 years versus ≥5 years), and baseline oral steroid dose. All subjects in the ITT population were included in the ITT analysis, whilst subjects who withdrew early or who had missing data were assigned to the lowest efficacy category. A sensitivity analysis assigning subjects to an efficacy category according to the dose reduction obtained by the time of withdrawal gave a similar result to the primary analysis. Analysis of the proportion of patients with specific reductions in oral steroid dose was performed using a binary logistic regression model with adjustment for covariates. The median percentage reduction in dose was analysed with the use of the Wilcoxon test. In SIRIUS, the rate of clinically significant exacerbations and rate of exacerbations requiring hospitalisation or ED visits were analysed using a negative binomial generalised linear model with a log-link function adjusting for covariates. Exacerbations requiring hospitalisation were not compared between treatment groups as there were no exacerbations requiring hospitalisation in the mepolizumab treatment arm.

The CS provides details of controlling for multiplicity across treatment comparisons and primary and secondary endpoints in DREAM and MENSA, presumably for the ITT analyses (CS p53-56). In SIRIUS no pre-specified multiplicity adjustment was performed.

4.2.2.4 Statistical methods for subgroup analyses

In DREAM and MENSA, exploratory multivariate modelling was performed to investigate baseline variables predictive of the overall number of exacerbations and of differential efficacy of

Table 1: Demographic characteristics for ITT populations (CS p66 and Appendix 8.3 and CSRs)

	DREAM (N=616)		MENSA (N=576)		SIRIUS (N=135)		
Demographic	**Placebo N=155**	**Mepolizumab All doses N=461**	**Placebo N=191**	**Mepolizumab Both doses N=385**	**Placebo N=66**	**Mepolizumab 100 mg SC N=69**	**Overall N=135**
Age, yr Mean (SD) Min, max	48.6 (11.28) 15, 74		50.1 (14.28) 12, 82		49.9 (10.30) 28, 70	49.8 (14.10) 16, 74	49.9 (12.34) 16, 74
Gender, (%) Female	63%		57%		45%	64%	55%
Race, (%) White	90%		78%		92%	97%	95%
Body Mass Index, kg/m^2 Mean (SD)	28.5 (5.95)		27.77 (5.830)		29.52 (6.047)	27.84 (5.895)	28.66 (6.007)
Duration of Asthma, yr Mean (SD)	19.1 (14.3)		19.9 (13.8)		20.1 (14.37)	17.4 (11.79)	18.7(13.13)
Blood Eosinophils (cell/µL) Geometric mean	250		290		230	250	NR
Exacerbations in previous year Mean (SD) ≥2 (%) ≥4 (%)	3.6 (3.1) 614 (99.7%) NR		3.6 (2.6) 575 (99.8%) 189 (33%)		2.9 (2.76) 45 (68%) 20 (30%)	3.3 (3.39) 46 (67%) 28 (41%)	3.1 (3.10) 91 (67%) 48 (36%)
≥1 Exacerbation requiring hospitalisation in previous year (%)	150 (24%)		109 (19%)		9 (14%)	14 (20%)	23 (17%)
On mOCS (%)	188 (31)		144 (25%)		66 (100%)	69 (100%)	135 (100%)
Screening Daily OCS Dose Mean (SD), mg	17.4 (16.77)		13.2 (11.89)		15.2 (6.71)	15.1 (9.31)	NR

CSR = clinical study report; ED = emergency department; mOCS = maintenance oral corticosteroids; NR = not reported; SC = subcutaneous; SD = standard deviation; yr = years

The ERG has tabulated the clinical effectiveness data showing the ITT population and the three additional populations for all three trials (and meta-analyses of these) side-by-side (Table 2 to **Error! Reference source not found.**). Some of these data are presented in various different sections of the CS, whilst some were provided by the company on request by the ERG. The subgroup analyses are described in Section 4.2.4.2, including those used as the basis for the GSK proposed populations.

Clinically significant exacerbations

Table 2 shows the rates of clinically significant exacerbations in all three trials (and meta-analysed across trials) in the ITT population, the two GSK populations and the stable mOCS population. Clinically significant exacerbations are defined as worsening of asthma requiring use of systemic corticosteroids and/or hospitalisation and/or emergency department (ED) visits. Use of systemic corticosteroids was defined as IV or oral steroid (e.g. prednisolone) for at least 3 days or a single intramuscular dose. For subjects on maintenance systemic corticosteroids, at least double the existing dose for at least 3 days was required to be categorised as a clinically significant exacerbation.

Clinical advisors to the ERG advised that exacerbations requiring either systemic corticosteroids or hospitalisation were more robust indicators of a severe exacerbation than ED visits, because some patients may visit the ED for minor reasons such as loss of an inhaler. Whilst clinically significant exacerbations as defined in the CS included ED visits these had to be confirmed as an asthma exacerbation. ED attendances for other reasons were excluded.

The rate ratios (RRs) for clinically significant exacerbations for mepolizumab (100mg SC and 75mg IV groups combined) vs. placebo, meta-analysed across MENSA and DREAM, were as follows (Table 2): RR=0.51 (95% CI 0.42, 0.62) in the ITT population; RR=0.41, 95% CI 0.31, 0.55) in the GSK PP; RR=0.35 (95% CI 0.25, 0.50) in the GSK PP excl. stable mOCS; and RR=0.55 (95% CI 0.32, 0.92) in the stable mOCS population. Therefore, as expected, results were more favourable for the GSK PP than the ITT population, and even more favourable for the GSK PP excl. stable mOCS, but less favourable for the stable mOCS group. In SIRIUS, the OCS-sparing study, RRs for exacerbations were slightly less favourable than in MENSA and DREAM: RR=0.68 (95% CI 0.47, 0.99) in the ITT population; RR=0.77 (95% CI 0.51, 1.17) in the GSK PP; RR=0.81 (95% CI 0.40, 1.64) in the GSK PP excl. stable mOCS; and RR=0.75 (95% CI 0.44, 1.29) in the stable mOCS population.

Table 2: Results for clinically significant exacerbations

	ITT				GSK PP				GSK PP excl. stable mOCS				Stable mOCS			
	Placebo	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**
	MENSA															
N	191	194	191	385	64	78	65		45	54	48		19	24	17	
Rate/year	1.74	0.83	0.93	0.877 (model)	2.65	1.32	1.06	1.206 (model)	3.10	1.22	1.20	1.213 (model)	1.4	1.3	0.63	
Rate ratio (mepo/pbo)		**0.47**	**0.53**	**0.50**		**0.50**	**0.40**	Not provided		**0.39**	**0.39**	Not provided		**0.93**	**0.45**	Not provided
95% CI		0.35, 0.64	0.40, 0.72	0.39, 0.65		0.32, 0.78	0.24, 0.67			0.23, 0.67	0.22, 0.68			0.42, 2.03	0.16, 1.24	
p-value		<0.001	<0.001	<0.001		0.002	<0.001			<0.001	<0.001			0.855	0.121	
	DREAM															
N	155		153	153	56		54	54	32		39	39	24		15	15
Rate/year	2.40		1.24	1.24	3.08		1.12	1.12	3.64		1.13	1.13	2.8		1.15	1.15
Rate ratio (mepo/pbo)			**0.52**	**0.52**			**0.36**	**0.36**			**0.31**	**0.31**			**0.41**	**0.41**
95% CI			0.39, 0.69	0.39, 0.69			0.24, 0.55	0.24, 0.55			0.18, 0.53	0.18, 0.53			0.19, 0.86	0.19, 0.86
p-value			<0.001	<0.001			<0.001	<0.001			<0.001	<0.001			0.019	0.019
	SIRIUS															
N	66	69		69	48	54		54	15	22		22	33	32		32
Rate/year	2.12	1.44		1.44	2.1	1.62		1.62	2.16	1.75		1.75	2.05	1.54		1.54
Rate ratio (mepo/pbo)		**0.68**		**0.68**		**0.77**		**0.77**		**0.81**		**0.81**		**0.75**		**0.75**
95% CI		0.47, 0.99		0.47, 0.99		0.51, 1.17		0.51, 1.17		0.40, 1.64		0.40, 1.64		0.44, 1.29		0.44, 1.29
p-value		0.042		0.042		0.222		0.222		0.556		0.556		0.298		0.298
	DREAM & MENSA meta-analysis															
N	346			538	120			197	77			141	43			56
Rate ratio (mepo/pbo)			Not requested	**0.51**			Not requested	**0.41**			Not requested	**0.35**			Not requested	**0.55**
95% CI				0.42, 0.62				0.31, 0.55				0.25, 0.50				0.32, 0.92
p-value				<0.001				<0.001				<0.001				0.023
	DREAM & MENSA & SIRIUS meta-analysis															
N					168			251	92			163	76			88
Rate ratio (mepo/pbo)			Not possible – different covariates				Not requested	**0.50**			Not requested	**0.42**			Not requested	**0.64**
95% CI								0.40, 0.64				0.30, 0.57				0.44, 0.93
p-value								<0.001				<0.001				0.019

Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. CI = confidence interval; GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; IV = intravenous; mOCS = maintenance oral corticosteroids; SC = subcutaneous

Pre-bronchodilator FEV_1

Table 3 shows the differences in scores for pre-bronchodilator FEV_1. The differences in FEV_1 for mepolizumab (100mg SC group) vs. placebo in MENSA were as follows: 98 ml (95% CI 11, 184) in the ITT population; 116 ml (95% CI -41, 272) in the GSK PP; and 107 ml (95% CI -95, 309) in the GSK PP excl. stable mOCS; no data were provided for the stable mOCS population. The CS states that these results reach clinical though not statistical significance (CS p88). Data from MENSA for the mepolizumab 75mg IV group were similar (Table 3).

In DREAM, the difference in FEV_1 for mepolizumab vs. placebo in the ITT population was smaller (61 ml) at 52 weeks than in MENSA (98ml and 100 ml; Table 3); the reason for this is not clear. Data for other DREAM populations, or for other sub-populations and meta-analyses, were not reported in the CS or requested by the ERG (Table 3).

Quality of life: St. George's Respiratory Questionnaire (SGRQ)

Error! Reference source not found. shows the differences in scores on the quality of life measure, the St. George's Respiratory Questionnaire (SGRQ). The differences in SGRQ scores for mepolizumab (100mg SC group) vs. placebo in MENSA were -7.0 (95% CI -10.2, -3.8) for the ITT population; -10.0 (95% CI -15.5, -4.5) for the GSK PP; -12.8 (95% CI -19.9, -5.8) for the GSK PP excl. c mOCS; and -1.2 (95% CI -10.8, 8.4) in the stable mOCS population. Data from MENSA for the mepolizumab 75mg IV group were similar. In SIRIUS, improvements for mepolizumab over placebo were approximately 5 to 6 units in all groups. SGRQ was not an endpoint in DREAM.

The CS states that the minimal clinically important difference (MCID) for SGRQ is 4 units (CS p87) and the differences in MENSA and SIRIUS range from 5 to 13 units in all groups, with the exception of the stable mOCS population in MENSA in which the improvement was only 1 to 3 units. The placebo groups improved from baseline by approximately 9 units and the mepolizumab groups by approximately 15-21 units, therefore the improvement was approximately two-fold greater in the mepolizumab than in the placebo groups.

Asthma Control Questionnaire (ACQ)

Error! Reference source not found. shows the differences in scores on the quality of life measure, the Asthma Control Questionnaire (ACQ). The differences in ACQ scores between mepolizumab (100mg SC and 75mg IV groups combined) vs. placebo, meta-analysed across MENSA and DREAM, were -0.34 (95% CI -0.48, -0.20) for the ITT population; -0.56 (95% CI -0.79, -0.33) for the GSK PP; -0.76 (95% CI -1.05, -0.47) for the GSK PP excl. stable mOCS; and -0.30 (95% CI -0.71, 0.10) in the stable mOCS population. The CS states that the MCID for ACQ is 0.5 units (CS p88), in which case, the ITT population would almost achieve clinical importance and the GSK population (but not the stable mOCS population) would show clinical

importance. The placebo groups improved from baseline by approximately 0.3 to 0.5 units and the mepolizumab groups by

Table 3: Results for pre-bronchodilator FEV_1 (ml)

	ITT				GSK PP				GSK PP excl. stable mOCS				Stable mOCS			
	Placebo	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**
	MENSA															
N	189	192	188	380	59	76	59		40	53	43					
LS mean (SE)	1907 (31.4)	2005 (31.1)	2007 (31.5)	2006 (22.1)	1844 (59.1)	1960 (52.8)	1975 (59.3)		1855 (75.4)	1962 (67.3)	2002 (72.9)					
LS mean change (SE)	86 (31.4)	183 (31.1)	186 (31.5)	184 (22.1)	118 (59.1)	234 (52.8)	249 (59.3)		114 (75.4)	221 (67.3)	261 (72.9)					
Difference (mepo-pbo)		**98**	**100**	**99**		**116**	**131**	Not provided		**107**	**148**	Not provided		Not requested	Not requested	Not requested
95% CI		(11, 184)	(13, 187)	(23, 174)		(-41,272)	(-35,296)			(-95,309)	(-59,355)					
p-value		0.028	0.025	0.010		0.147	0.120			0.295	0.160					
	DREAM															
N	127		129	129												
LS mean (SE)	1942 (37.7)		203 (37.6)	2003 (37.6)												
LS mean change (SE)	60 (37.7)		121 (37.6)	121 (37.6)												
Difference (mepo-pbo)			**61**	**61**			Not provided	Not provided			Not provided	Not provided			Not requested	Not requested
95% CI			(-39, 161)	(-39, 161)												
p-value			0.229	0.229												
	SIRIUS															
N	62	66		66	46	52		52								
LS mean (SE)	1955 (56.5)	2070 (55.1)		2070 (55.1)	1896 (66.2)	2036 (62.3)		2036 (62.3)								
LS mean change (SE)	-4 (56.5)	111 (55.1)		111 (55.1)	17 (66.2)	157 (62.3)		157 (62.3)								
Difference (mepo-pbo)		**114**		**114**		**140**		**140**		Not requested		Not requested		Not requested		Not requested
95% CI		(-42, 271)		(-42, 271)		(-41, 321)		(-41, 321)								
p-value		0.151		0.151		0.129		0.129								
	Meta-analyses not provided in the CS or requested by the ERG															

Analysis performed using mixed model repeated measures with covariates of baseline, region, treatment and visit, plus interaction terms for visit by baseline and visit by treatment group. CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; IV = intravenous; ml = millilitres; mOCS = maintenance oral corticosteroids; SC = subcutaneous; SE = standard error

eosinophils was not found to be statistically significant at the 5% level and so there is likely to be considerable uncertainty associated with the illustrated predicted rates.

The number of previous exacerbations is also shown to be prognostic of treatment effect, and so the blood eosinophil threshold required to obtain a 30% reduction in the rate of exacerbation will vary according to this covariate. In response to a request from the ERG for clarification, the company provided relative cut-offs separately according to the number of previous exacerbations (Table 4). Using data from DREAM (n=286, 46% of total) and MENSA (n=245, 43% of total), for patients with 2 exacerbations a threshold of between 350 and 400 cells/ µL and between 100 and 150 cells/ µL, respectively would be required to achieve the specified reduction in rate. For patients with ≥4 exacerbations (representative of the GSK PP) the reported threshold is <50 cells/ µL in DREAM and between 50 and 100 cells/ µL in MENSA.

Table 4: Eosinophil levels that predict a 30% reduction in exacerbations conditional on exacerbations in the previous year (clarification response A15)

Exacerbations in previous year	Eosinophil level that predicts a 30% reduction	
	Study DREAM	Study MENSA
2 exacerbations	Between 350 and 400 cells/ µL	Between 100 and 150 cells/ µL
3 exacerbations	Between 100 and 150 cells/ µL	Between 50 and 100 cells/ µL
≥4 exacerbations	<50 cells/µL	Between 50 and 100 cells/ µL

The rate of exacerbations according to blood eosinophil level in MENSA is shown in Table 5 (adapted from CS p103). This compares two different options for a blood eosinophil threshold: ≥150/µL at screening, or ≥300/µL in the previous 12 months. Clinical advisors to the ERG advised that a threshold of 300 cells/µL would appear more appropriate since 150 cells/µL was a relatively low count which was within the normal range, and that a threshold observed anytime in the previous 12 months would seem more appropriate than one observed exactly at the point of screening since eosinophil level can fluctuate.

Patients with ≥150/µL at screening had greater reduction in exacerbations for mepolizumab vs. placebo (RR=0.46 and 0.38 for 75mg IV and 100mg SC respectively) than patients with <150/µL (RR=0.94 and 0.91). The company use these results as the basis for focussing on patients with ≥150/µL at screening.

However, the results observed for subgroups based on a threshold of ≥300/µL in the previous 12 months were not intuitive for the following two reasons:

1) Exacerbation rates in the placebo groups were lower for patients with ≥300/µL in the previous 12 months compared with patients with <300/µL (1.64 vs. 1.89), and
2) Patients with ≥300/µL in the previous 12 months had a smaller reduction in exacerbations for mepolizumab vs. placebo (RR=0.69 and 0.57) than patients with <300/µL (RR=0.27 and 0.27), which is not intuitive.

It should be noted that patients with eosinophils <300/µL in the past year would all have had eosinophils ≥150/µL at screening, while patients with ≥300/µL in the past year may or may not have had ≥150/µL at screening. This is due to the MENSA inclusion criteria in which patients were required to have eosinophils ≥150/µL at screening and/or ≥300/µL in the past year. This may partially account for the above findings.

Table 5: Analysis of rate of clinically significant exacerbations by blood eosinophil criteria (MENSA, adapted from CS p103 Table 44)

Blood eosinophil inclusion criteria group	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
Criterion: ≥300/µL in the previous 12 months			
<300/µL in the previous 12 months			
N Exacerbation rate/year	70 1.89	61 0.51	48 0.50
RR (mepolizumab/placebo) 95% CI		**0.27** 0.15, 0.51	**0.27** 0.14, 0.52
≥300/µL in the previous 12 months			
N Exacerbation rate/year	121 1.64	130 1.13	146 0.94
RR (mepolizumab/placebo) 95% CI		**0.69** 0.49, 0.98	**0.57** 0.41, 0.80
Criterion: ≥150/µL at screening[1]			
<150/µL at screening			
N Exacerbation rate/year	21 1.31	30 1.23	35 1.20
RR (mepolizumab/placebo) 95% CI		**0.94** 0.43, 2.07	**0.91** 0.44, 1.90
≥150/µL at screening			
N Exacerbation rate/year	167 1.75	155 0.81	155 0.67

Previous exacerbations threshold

For DREAM, the CS states that a planned subgroup analysis showed greater decreases in exacerbations in the mepolizumab groups (vs. placebo) in subjects who had previously experienced more exacerbations (**Error! Reference source not found.**, CS p108). Previous exacerbations (in the GSK PP and the subgroup analyses) are defined as exacerbations requiring systemic corticosteroids (or for subjects on mOCS, a two-fold or greater dose increase) and/or hospitalisations or ED visits. This is contrary to the definition supplied in the company's clarification response, but is the definition provided in the Fact Check process.

The CS states that the interaction between the number of previous exacerbations and treatment group was potentially significant (p=0.014); this indicates that there was a potentially significant difference in exacerbation reduction for patients according to the number of prior exacerbations. For patients receiving mepolizumab 75mg, the RRs for exacerbations vs. placebo were 0.86 (2 previous exacerbations); 0.42 (3 previous exacerbations); and 0.36 (4 previous exacerbations). However, although the RRs appear more favourable for subgroups with 3 or ≥4 than for 2 previous exacerbations, there appears to be little difference in RR between those with 3 and ≥4 previous exacerbations (**Error! Reference source not found.**).

For MENSA, exacerbation rates according to previous exacerbation history are shown in **Error! Reference source not found.** (CS p80). The rate of exacerbations in the placebo arm increases as the number of exacerbations in the previous year increases: from a rate of 1.09 for 2 previous exacerbations rising to 3.22 for ≥4 previous exacerbations. For the mepolizumab 75mg IV and 100mg SC groups, the RRs vs. placebo were 0.57 and 0.53 (2 previous exacerbations); 0.56 and 0.30 (3 previous exacerbations); and 0.40 and 0.44 (4 previous exacerbations). The combination of these data indicate that the greatest absolute number of exacerbations prevented would be in the groups with 4 or more previous exacerbations.

Table 6: **Analysis of rate of clinically significant exacerbations by previous omalizumab use (ITT population, MENSA, CS Table 48)**

Previous Omalizumab use	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
Yes			
N Exacerbation rate/year	21 2.36	29 0.65	25 1.40
Comparison vs. placebo			
RR (mepolizumab/placebo) 95% CI		0.27 0.12, 0.65	0.59 0.28, 1.26
No			
N Exacerbation rate/year	170 1.62	162 0.99	169 0.74
Comparison vs. placebo			
RR (mepolizumab/placebo) 95% CI		0.61 0.45, 0.84	0.46 0.33, 0.63

CI = confidence interval; IV = intravenous; SC = subcutaneous

4.2.4 Open-label extension studies

4.2.4.1 Description of open-label extension studies

The CS provided data on two open-label, non-randomised, non-controlled extension studies enrolling patients completing the pivotal RCTs (Table 7, CS p154). All patients in these studies received mepolizumab 100mg SC:

- COSMOS, which enrolled patients from MENSA and SIRIUS (completed). Patients either continued mepolizumab without interruption or switched from placebo to mepolizumab. The study duration was 52 weeks (in addition to the initial RCT duration).
- COLUMBA, which enrolled patients from DREAM (ongoing; interim analysis results used with data cut-off in February 2014). Patients had a ≥12 month treatment break before starting or re-starting mepolizumab. The treatment duration with mepolizumab will be up to 3.5 years.

The CS also provides details of an additional non-randomised study, which the CS states was considered less relevant and was not discussed further:

- PK/PD study (MEA114092[40]) evaluating the PK/PD relationship for different doses and formulations of mepolizumab (75mg IV; 12.5mg, 125mg and 250mg SC) in severe asthma patients on high dose ICS with blood eosinophils >300/µL or ≥200/µL within 12 months of screening and >300/µL or ≥200/µL at screening.

Table 7: Open-label extension studies COSMOS and COLUMBA (adapted from CS Tables 74 and 75)

Trial	Intervention	Population	Outcomes	Duration
COSMOS (MEA115661)	• SC Mepolizumab 100mg • Patients previously on mepolizumab continued without interruption; patients previously on placebo started on mepolizumab	• Patients completing MENSA or SIRIUS • Receiving controller medication	Long-term safety and efficacy data	52 weeks (in addition to MENSA or SIRIUS RCT duration of 32 or 24 weeks)
COLUMBA (MEA115666)	• SC Mepolizumab 100mg • Cessation and re-start of mepolizumab with ≥12 month treatment break • Treatment for up to 3.5 years	• Patients having received ≥2 doses study drug in DREAM • Receiving controller medication	Long-term safety and efficacy data	Up to 3.5 years (following ≥12 month treatment break after 52 week DREAM trial)

SC = subcutaneous

A total of 998 patients have been enrolled in COSMOS (N=651) and COLUMBA (N=347; Table 8). More than half of the patients who participated in DREAM (347/616, 56%) enrolled in COLUMBA, with a ≥12 month treatment break between the two studies. Most patients from MENSA (525/576, 91%) and SIRIUS (126/135, 93%) elected to continue treatment and directly rolled over into COSMOS. All patients received mepolizumab 100mg SC in the open-label extension regardless of their treatment assignment in the double-blind parent study. COLUMBA started before COSMOS, thus patients have longer treatment exposure in this study. As of the February 28th, 2014 data cut-off date for the interim analysis, 96% of patients were continuing treatment and there were 643 patient years of exposure. The most common reasons for premature withdrawal from the open-label studies were AEs and withdrawal of consent (1% for each). The As Treated (AT) population consisted of all subjects who received at least one dose of mepolizumab; this represents the primary population for all summaries of efficacy and safety measures.

The demographics for patients in COSMOS and COLUMBA were similar to those of the RCTs from which patients enrolled (Table 9).

Table 8: Patient numbers in open-label extension studies COSMOS and COLUMBA (CS p153-4)

	Receiving mepolizumab 100mg SC	
Trial	**COLUMBA (interim)**	**COSMOS (final)**
% enrolling from RCTs	From DREAM: 347/616 (56%)	From MENSA: 525/576 (91%) From SIRIUS: 126/135 (93%)
Previous treatment		Previous mepolizumab: 414 Previous placebo: 237
N enrolled	**347**	**651**
Withdrawn	22 (6%)	66 (10%)
Continuing treatment (interim)	325 (94%)	N/A
Completed	N/A	585 (90%)
Primary reason for withdrawal, N (%):		
Adverse event	8 (2)	11(2)
Withdrew consent	8 (2)	14 (2)
Lack of efficacy	0	19 (3)
Protocol deviation	2 (<1)	8 (1)
Physician decision	1 (<1)	9 (1)
Lost to follow-up	2 (<1)	3 (<1)
Met protocol stopping criteria	1 (<1)	2 (<1)

SC = subcutaneous

Table 9: Demographics for COSMOS and COLUMBA, ITT populations (CS p152-3)

Demographic	COLUMBA (N=347)	COSMOS (N=651)
Age, yr Mean (SD)	52.2 (10.7)	51.1 (13.9)
Gender, (%) Female	65	55
Race, (%) White	92	81
Body Mass Index, kg/m^2 Mean (SD)	28.62 (6.10)	28.02 (5.85)

SD = standard deviation

4.2.4.2 Clinical effectiveness results of open-label extension studies COSMOS and COLUMBA

Rate of exacerbations

The rate of exacerbations per year in COLUMBA was 0.67 (**Error! Reference source not found.**), which is lower than the rate of 1.24 in the mepolizumab group for the DREAM ITT population (Table 2). The rate of exacerbations per year in COSMOS was 0.93 (**Error! Reference source not found.**), which is similar to the rate of 0.88 in the mepolizumab group for the MENSA ITT population but slightly higher than the rate of 0.68 for the SIRIUS ITT population (Table 2). The number of patients experiencing ≥1 exacerbation was 151/347 (44%) in COLUMBA and 311/651 (48%) in COSMOS.

4.2.5 Safety of mepolizumab

The CS provided a review of safety evidence and AEs for mepolizumab. Results were presented for the placebo-controlled trials (DREAM, MENSA and SIRIUS) and the non-randomised, non-controlled, open-label extension studies (COSMOS and COLUMBA). Data collection has been completed for COSMOS but is ongoing for COLUMBA (data cut-off of 28th February 2014). The CS provided safety data collated across the three RCTs. The ERG requested additional data on AEs of special interest; these were provided by the company for each trial separately (clarification response Question A12) and collated across trials by the ERG.

4.2.5.1 Rates of AEs

AEs with relative risk of 1.5 or greater for mepolizumab vs. placebo in RCTs: AEs for which the risk was at least 1.5 times as great for mepolizumab vs. placebo are shown in Table 10 (ordered by relative risk). Eczema was significantly and five times more frequent in the mepolizumab arms than the placebo arms (2.5% vs. 0.5%, RR=5.34, 95% CI 1.25 to 22.78). Nasal congestion and dyspnoea were more than twice as likely to be experienced by subjects taking mepolizumab compared with those taking placebo. Allergic rhinitis and urinary tract infections were approximately 1.6 times as common in the mepolizumab vs. placebo groups.

Table 10: Adverse events with relative risk of 1.5 or greater for mepolizumab vs. placebo for DREAM, MENSA and SIRIUS (adapted from CS Table 89)

Event	Treatment	N	Number (%) with Event		Adjusted Cumulative Proportion [1]	Relative Risk	(95% CI) [2]
Eczema	Placebo	412	2	0.50%	0.50%		
	All Doses	915	23	2.50%	2.60%	5.34	(1.25, 22.78)
Nasal congestion	Placebo	412	4	1.00%	1.00%		
	All Doses	915	24	2.60%	2.50%	2.62	(0.89, 7.72)
Dyspnoea	Placebo	412	4	1.00%	1.10%		
	All Doses	915	23	2.50%	2.30%	2.2	(0.78, 6.20)
Rhinitis allergic	Placebo	412	7	1.70%	1.70%		
	All Doses	915	27	3.00%	2.80%	1.64	(0.70, 3.85)
Urinary tract infection	Placebo	412	9	2.20%	2.10%		
	All Doses	915	32	3.50%	3.40%	1.63	(0.77, 3.47)

[1] Adjusted using Cochran-Mantel-Haenszel weights [2] Calculated using the Cochran-Mantel-Haenszel method. CI = confidence interval

AEs with a frequency of 5% or greater for mepolizumab in RCTs: AEs with a frequency of ≥5% for mepolizumab are shown in **Error! Reference source not found.** (ordered by relative risk). Nasopharyngitis and headache had a frequency of more than 20% in the mepolizumab group, which was similar to the placebo groups. All AEs in this category had fairly similar frequencies in the mepolizumab and placebo groups, all with relative risks of less than 1.3.

The ERG notes that the longest follow-up for which data are provided for mepolizumab 100mg SC is 84 weeks (in MENSA then COSMOS) although eventually data for up to 3.5 years will be available from COLUMBA. Given that treatment might be expected to be life-long, there is therefore uncertainty regarding the long-term safety of mepolizumab.

4.2.5.7 Summary of safety data

Mepolizumab appears to be generally well-tolerated in severe eosinophilic asthma patients, with the exception of possible increased risks of eczema, nasal congestion, dyspnoea and injection site reactions with mepolizumab. Hypersensitivity reactions, infections and malignancy occurred at similar rates with mepolizumab and placebo. Cardiac events occurred at similar rates with mepolizumab and placebo, whilst rates of serious cardiac events and serious CVT events were slightly higher for mepolizumab (though event rates were low). In terms of SAEs, there were two cases each of herpes zoster, hypertension and myocardial ischaemia for mepolizumab, versus none for placebo.

In both the placebo-controlled trials and open-label studies, 5%-6% of patients treated with mepolizumab 100mg SC developed anti-mepolizumab antibodies. There is also no evidence for the long-term safety of mepolizumab 100mg SC beyond 84 weeks (in MENSA then COSMOS) although eventually data for up to 3.5 years will be available from COLUMBA.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Omalizumab is a relevant comparator for patients who exhibit both allergic (IgE) and eosinophilic phenotypes of severe asthma and who would be potentially eligible for either medication. As there are no head-to-head trials comparing mepolizumab and omalizumab, the company undertook a network meta-analysis (NMA) to compare the two treatments indirectly by synthesising trials comparing either drug to a common comparator, standard of care (CS Section 4.10 p127-149).

Search strategy for NMA

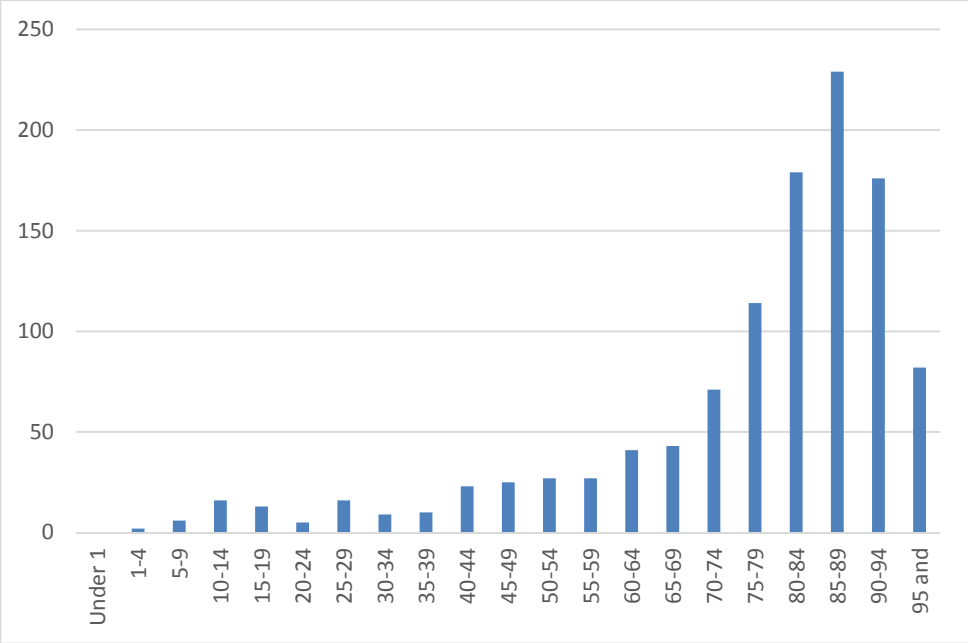
The CS reports a literature search for studies of both mepolizumab and omalizumab (described in Section 4.1). The ERG considers the search strategy to be appropriate and would expect it to identify relevant studies of mepolizumab and omalizumab.

Study selection criteria for NMA

The inclusion and exclusion criteria for the NMA are not very clearly laid out in the CS and so are summarised below by the ERG.

Figure 1 shows the deaths caused by asthma registered in England and Wales in 2014 stratified by age as reported by the Office for National Statistics.[48] These data confirm that asthma-related mortality increases markedly after the age of 65 years with 80% of the asthma-related deaths occurring in people aged 65 years or older.

Figure 1: Asthma deaths in England and Wales, 2014. Source: Office for National Statistics[48]



The NRAD report analyses 195 asthma-related deaths. The categories of locations of death within the NRAD report were: home (private address) 41%; hospital, arrest in hospital 30%; hospital, pre-hospital arrest 23%; nursing / residential home 3%; holiday 2%; and other 1%.

The company's model assumes that all deaths in Watson *et al*. would be categorised as 'hospital, arrest in hospital', which account for the 30% of deaths in the NRAD report, and that therefore the total number of deaths would be 100/30 times greater than those reported in Watson *et al*. These additional deaths were divided between those exacerbations that required an ED visit (23/70) and those assumed to only require an OCS burst (47/70). The distribution of deaths amongst the three groups of exacerbations: hospitalisation; ED visit and OCS burst were assumed constant and independent of the number of deaths reported in hospital. The ERG notes that should any of the deaths in Watson *et al*. be assignable to the 'hospital, pre-hospital arrest' category, then the number of deaths due to asthma exacerbations would be overestimated. However, this is unlikely as it appears that all deaths were reported after admission.

5.2.11.3 Scenario analysis: OCS sparing

The company performed a scenario analysis that attempted to include long-term costs and consequences of maintenance OCS. For that purpose, the company undertook a study using the Clinical Practice Research Datalink (CPRD) to estimate the dose-dependent risk of developing 6 AEs associated with systemic corticosteroid therapy: myocardial infarction; glaucoma; diabetes; cataracts; osteoporosis; and peptic ulcer.

The company used the data collected during SIRIUS to calculate the reduction in OCS use in two ways: using the percentage of patients that managed a total reduction of OCS and the median percentage of OCS reduction. The company stated that the median was used instead of the mean due to the skewedness of the distribution, although the ERG notes that it is typical to use mean values in economic evaluations. The ERG notes that using the percentage of patients that had managed to discontinue OCS treatment was likely to underestimate the OCS dose reduction. The ERG considers that it would have been more appropriate to use population-dependent data instead of assuming that the reductions in OCS use and the proportion of patients on mOCS in the ITT population was applicable for all three populations. The company assumes that the OCS reduction data gathered in SIRIUS are applicable for omalizumab. The ERG notes that data relating to the proportion of patients discontinuing OCS are available in the Assessment Group's report for the omalizumab MTA and are markedly different from those for mepolizumab: 14.5% of patients discontinued OCS treatment in SIRIUS compared with 32.2% of omalizumab patients who were on baseline mOCS in the EXALT trial.[45] However, a direct comparison of discontinuation percentages from the open label EXALT study and SIRIUS has to be taken with caution.

The time horizon used to calculate the costs and consequences of AEs associated with systemic OCS was 10 years, matching the biologic treatment duration in the base case analysis. The ERG notes the use of a time horizon shorter than lifetime is likely to underestimate the benefits of OCS sparing, as some of the diseases avoided during the treatment are chronic and therefore would have been suffered by the patients for the rest of their lives, or these diseases could develop or become symptomatic beyond the 10-year time horizon.

The company uses data from MENSA to calculate exacerbation rates in mepolizumab patients in addition to using the OCS usage reduction data from SIRIUS. The ERG notes that this, in isolation, is likely to overestimate the aggregate benefits of mepolizumab, as exacerbation rates might not decrease as much when reducing OCS usage.

5.2.11.4 Sensitivity analyses performed in response to clarification questions raised by the ERG

The ERG noted that the comparison between the ICERs for the GSK PP and the GSK PP excl. stable mOCS suggests that there is a subgroup (mOCS users with <4 exacerbations) included in the GSK PP. This subgroup accounts for approximately 30% of the GSK PP in the MENSA trial and as stated by GSK *"this population will appear less cost-effective compared to the GSK proposed population when excluding mOCS users who did not achieve the required 4 exacerbations in the previous year, despite representing a more severe population."* During clarification, the ERG requested that a separate analysis be performed to estimate the ICER for the use of mepolizumab in mOCS users with a blood eosinophil count of ≥150 cells/μL at initiation of treatment and <4 exacerbations (question B1). The company performed the requested analysis and reported an ICER of £78,716 per QALY gained (see Table 11). The increase in the ICER was due to: (i) a lower exacerbation rate; (ii) fewer exacerbations requiring hospitalisation (and therefore lower asthma related mortality), and; (iii) and a smaller difference in the utilities between mepolizumab and the comparator in this subgroup.

Table 11: Results of the subgroup analysis for mOCS users with a blood eosinophil count of ≥150 cells/μL at initiation of treatment and <4 exacerbations

	Total Cost	Δ Cost	Total QALY	Δ QALY	ICER (vs.)
Mepolizumab + Standard of Care	[redacted]	-	[redacted]		
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	£78,716

The ERG was also concerned that the age stratification of asthma related mortality rates in Watson *et al.*[1] could lead to an overestimation of deaths due to asthma in the early years within the model. In reply to the ERG's clarification letter, the company performed two exploratory analyses which the company stated should be interpreted with caution. These were combining the asthma-related mortality rates reported by Watson *et al.*[1] and Roberts *et al.*,[2] using two different approaches: by applying the rate ratios derived from comparing the rate for the 35-44 age band with the other age bands as reported by Roberts *et al.* to the mortality rate reported by Watson *et al.* for the 17-44 age band (option 1); and assuming the same number of exacerbations across the three age bands and fitting the total deaths reported by Watson *et al.* in a way that the relative RRs of the different age bands were similar to those reported by Roberts *et al.* (option 2). The ERG preferred option 2: the resultant assumed mortality rates using this approach are shown in

Table 12.

Table 12 Mortality rates calculated based on the number of deaths and hospitalizations reported for the ≥45 group in Watson *et al.*[1] and the ratios in Roberts *et al.*[2] (option 2)

Age group	Roberts *et al.*[2]		Watson *et al.*[1]			Watson *et al.*[1] + Roberts *et al.*[2]			
	p	ratio	p	n	N	p	ratio	n	N
45-54	0.0045		0.0248	177	7143	0.0076		18	2381
55-64	0.0127	2.84				0.0214	2.83	51	2381
≥65	0.0278	6.20				0.0454	6.00	108	2381

The ERG considers that the exacerbation rates used in the model for patients who meet the continuation criteria could be inappropriate: these rates were measured in the MENSA trial shortly after the beginning of the treatment, based on a 16-week time span and therefore might not be representative of the long-term effectiveness of mepolizumab and may be affected by seasonality; further, there may be a regression to the mean. In contrast, in the COSMOS study, the rates were measured in a period of a full year in patients that had already been on mepolizumab for 32 weeks. The company acknowledged in their clarification responses (question A19) that the continuation criteria in COSMOS were consistent with recommendations in the SmPC. Additionally, the percentage of MENSA patients that went on to participate in COSMOS is almost identical to those meeting the continuation criteria in the ITT population of MENSA (90.1% vs 90.9%). For these reasons, during the clarification process, the ERG requested the company to undertake an analysis whereby exacerbation rates from COSMOS were used in the model as exacerbation rates for patients on mepolizumab who met the continuation criteria (question B4). However, the company did not undertake the requested analysis and argued instead that the exacerbation rate measured in COSMOS in patients who had been treated with mepolizumab during MENSA (rate=0.9) was similar to that measured in the ITT population in MENSA (rate=0.877). The ERG agreed in the similarity of these two rates but note that they are markedly different to the rate used in the model for patients on mepolizumab meeting the continuation criteria (rate=0.55 in the ITT population).

The ERG also requested a scenario analysis based on the exacerbation rates and utilities recorded in the DREAM trial and analyses where exacerbation rates were calculated through a meta-analysis of data gathered in MENSA and DREAM, both using EQ-5D utilities (DREAM) and the SGRQ-mapped utilities (MENSA). The results of this request were provided to the ERG within the company response.

The ERG believes that the results of the SIRIUS trial are particularly relevant, since it assesses the effectiveness of mepolizumab in patients on mOCS. The GINA guidelines[58] specify that "patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered" should be considered in Step 5, which usually entails maintenance OCS. Bousquet *et al.* consider that having more than two exacerbations in a year

is sufficient for asthma to be categorised as "poorly controlled".[59] Considering that the patients in the GSK PP that are not on maintenance OCS suffered at least four such exacerbations in the previous year, the ERG believes that the inclusion of mOCS for these patients should have been considered. Therefore, the ERG believes that mOCS is a potentially relevant comparator for the GSK PP in addition to the comparator of usual Step 4 treatment and that the SIRIUS trial is representative of this comparison. Consequently, the ERG requested analyses based on the exacerbation rates and utilities recorded in SIRIUS, but the company claimed there was no time within the STA process to perform a full reanalysis and undertook a scenario analysis where utilities estimated from SGRQs gathered in SIRIUS were used while using the exacerbation rates from MENSA. The company did not report results for the GSK PP excl. stable mOCS claiming that there were too few patients in this sub-population in SIRIUS.

Table 13: Utilities measured in SIRIUS and used in the company's exploratory analysis

	Full Trial Population (ITT from SIRIUS)	GSK PP excl. stable mOCS	GSK PP
	Mean (SE)	Mean (SE)	Mean (SE)
Add-on mepolizumab: All patients	0.710 (0.027)	N/A	0.711 (0.028)
SoC	0.706 (0.026)	N/A	0.718 (0.029)
Add-on mepolizumab: Meeting CC	0.716 (0.029)	N/A	0.696 (0.036))

SoC: Standard of care; CC: continuation criteria

The ERG consider that the continuation criteria proposed by the company (i.e. continue on treatment unless the exacerbation rate increases) imply that a subgroup of patients could remain on treatment even when experiencing no improvement. The ERG requested that the company present exploratory analyses to assess the impact on the ICER of the amending the continuation criteria such that patients had to improve by a certain amount (as gauged by reduction of exacerbations or OCS use). The company replied that it did "not believe it is appropriate" to quantify the level of improvement in terms of reduction of exacerbations because for patients "on maintenance OCS, who may be less likely to experience a further reduction in exacerbations", mepolizumab "provides the opportunity to reduce OCS exposure". However, in response to this request, the company reported results of exploratory analyses varying both the percentage of patients meeting the continuation criteria and the time to continuation assessment. The ERG noted that the validity of these exploratory analyses was

The ERG would have preferred a base case analysis that was not restricted by the blood eosinophil count at screening but which still maintained a requirement for four or more exacerbations. However, the ERG did not have access to the necessary data and did not request these data or the corresponding analysis to be undertaken by the company as part of the clarification process. As such, the exploratory analyses presented in this section do not fully represent the true ERG base case.

The ERG modified some of the settings of the company's base case analysis for its analyses. The exploratory analyses include the following amendments:

1) Use of directly measured EQ-5D scores instead of the scores mapped from SGRQ (therefore adhering to the NICE Reference Case and the preference of the Appraisal Committee in the omalizumab MTA);
2) Use of asthma-related mortality rates estimated by the company combining the data from Watson *et al.*[1] and Roberts *et al.*[2] in response to the ERG's clarification questions (described as Option 2 in Section 5.2.11.4);
3) Based on feedback from the clinical experts to the ERG, assuming that a stopping rule of 10 years was inappropriate and that no fixed stopping rule would be applied;
4) Using the average length of the exacerbations measured in MENSA (12.68, 10.41, and 20.70 days for exacerbations requiring OCS burst, ED visit, and hospitalisation respectively) instead of the time over which EQ-5D was captured in Lloyd *et al.* [51] (28 days);
5) Setting the exacerbation rates for those meeting the continuation criteria to those observed in the COSMOS study. However, the ERG did not have access to the exacerbation rates for the GSK PP and GSK PP excl. stable mOCS in COSMOS. In order to overcome this limitation, the ERG estimated these rates based on the exacerbation rate measured in COSMOS in patients that had been on mepolizumab during MENSA, as reported in the company's clarification response (rate=0.90). The ERG estimated the rates for the GSK PP and GSK PP excl. stable mOCS by multiplying this rate by the RRs between rates of the ITT population and GSK PP and GSK PP excl. stable mOCS as used in the base case. The resulting rates are shown in Table 14.

Table 14: Exacerbation rates for patients on mepolizumab after continuation assessment based on COSMOS

	ITT		GSK PP excl. stable mOCS		GSK PP	
	Annual rate	4-weekly rate	Annual rate	4-weekly rate	Annual rate	4-weekly rate
Base case	0.550	0.042	0.723	0.056	0.645	0.050
COSMOS	0.900	0.069	1.183†	0.091	1.054‡	0.081

† 0.9*(0.723/0.550)
‡ 0.9*(0.645/0.550)

Table 15: Results of the exploratory analyses undertaken by the ERG

Scenario Number		ITT population					GSK PP excl. stable mOCS					GSK PP				
		Total cost (£)	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (£)**	**Total cost (£)**	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (£)**	**Total cost (£)**	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (£)**
	Company's base case (probabilistic)															
	Mepo	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	31,692	[redacted]	[redacted]	[redacted]	[redacted]	15,478	[redacted]	[redacted]	[redacted]	[redacted]	19,511
1	Source of health state utilities: EQ-5D (DREAM)															
	Mepo	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	40,392	[redacted]	[redacted]	[redacted]	[redacted]	18,429	[redacted]	[redacted]	[redacted]	[redacted]	20,863
2	Asthma-related mortality: Watson *et al.* / Roberts *et al.* (company option 2)															
	Mepo	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	42,728	[redacted]	[redacted]	[redacted]	[redacted]	20,735	[redacted]	[redacted]	[redacted]	[redacted]	27,544
3	Biologic treatment duration: Life time															
	Mepo	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	32,130	[redacted]	[redacted]	[redacted]	[redacted]	15,571	[redacted]	[redacted]	[redacted]	[redacted]	19,763
4	Source of duration of utility decrement for an exacerbation: MENSA															
	Mepo	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	32,480	[redacted]	[redacted]	[redacted]	[redacted]	15,690	[redacted]	[redacted]	[redacted]	[redacted]	19,963
5	Exacerbation rates for patients meeting the CC based in COSMOS															
	Mepo	[redacted]		[redacted]			[redacted]		[redacted]			[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	37,190	[redacted]	[redacted]	[redacted]	[redacted]	17,240	[redacted]	[redacted]	[redacted]	[redacted]	22,239

	Combination of company's scenario analyses 1-4 (probabilistic)															
	Mepo															
	SoC					59,094					28,184					30,410
	ERG's base case 1-5 (probabilistic)															
	Mepo															
	SoC					72,596					33,520					35,440

CC = continuation criteria; N/A = not available

The ERG noted that the GSK PP included a subgroup (the stable mOCS) for which the company estimated an ICER of £78,716 per QALY gained. An exploratory analysis was conducted by the ERG that amended the company's estimate by using scenario numbers 2-5 in Table 15. The utility estimate was held at the values reported by the company even though these were mapped from SGRQ values, because direct EQ-5D values were not available for this sub-population. This resulted in an ICER for the stable mOCS population of £167,778 per QALY (see Table 16).

Table 16: Results for the stable mOCS population based on the ERG's base case analysis

	Total Cost (£)	**Δ Cost (£)**	**Total QALY**	**Δ QALY**	**ICER (£)**
Mepolizumab + standard of care	[redacted]		[redacted]		
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	167,778

The ERG performed exploratory analyses using data collected in the SIRIUS trial combined with scenario numbers 2-5 in Table 15. The utility estimates was held at the values reported by the company even though these were mapped from SGRQ values; this was because direct EQ-5D values were not available for this sub-population. The company reported population-specific utilities that were mapped from SGRQ values, but these appeared counterintuitive as SoC have a higher utility value than patients on mepolizumab and the utility for all patients on mepolizumab was higher than for patients meeting the continuation criteria (Table 13). These exploratory resulted in the ICERs shown in

Table 17. Both ICERs were greater than £75,000 per QALY gained. The GSK PP results are subject to considerable uncertainty due to a small patient population; the population in SIRIUS who would be categorised in the GSK PP excl. stable mOCS group were too small for meaningful analyses to be undertaken.

These results imply that at least [redacted] extra QALYs would have to be gained from OCS sparing for the ICER to be under £30,000 for QALY gained. The corresponding number of additional QALYs required to have an ICER under £20,000 per QALY gained was [redacted].

Table 17: Result of the exploratory analyses based on SIRIUS*

	ITT					GSK PP				
	Total cost (£)	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (£)**	**Total cost (£)**	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (£)**
ERG's base case + utilities and exacerbation rates from SIRIUS (population-specific utilities)										
Mepo	[redacted]					[redacted]				
SoC	[redacted]				84,700	[redacted]				147,637
ERG's base case + utilities and exacerbation rates from SIRIUS (using ITT utilities)										
Mepo	[redacted]					[redacted]				
SoC	[redacted]				84,700	[redacted]				79,804

*All patients in the SIRIUS trial were dependent on maintenance OCS

The ERG undertook analyses comparing mepolizumab add-on to omalizumab add-on in those patients on mOCS (

Table 18). The ERG explored the impact of alternative assumptions regarding the list price of omalizumab (using the one reported in the omalizumab MTA rather than that reported in the CS) and the use of exacerbation RRs applicable to the mOCS population rather than the ITT population (given that NICE issued a recommendation to treat with omalizumab only patients who were on maintenance OCS). The ERG also preferred the use of the random effects model for the NMA rather than the fixed effects model. Finally, the ERG combined these three alternative assumptions. This represented the ERG's base case and resulted in an ICER for omalizumab compared with mepolizumab of £43,084. It is worth noting that these analyses were performed using the PAS price of mepolizumab and the list price of omalizumab. The ERG repeated these same analyses using the PAS price for both mepolizumab and omalizumab and presented these results in a confidential appendix. The ERG comment that if there has been an increase in drug costs for mepolizumab (based on changes in weight and baseline IgE levels) without an increase in effectiveness then including Scenario A would be unfavourable to mepolizumab. For completeness the estimated ICER of mepolizumab compared with SoC calculated from the NMA is also shown in Table 18.

Table 18: Results of exploratory analyses ERG omalizumab

Scenario Number		Mepo	Omalizumab	Mepo vs. omalizumab	SoC	Mepo vs. SoC
	Deterministic results incorporating scenario numbers 1-5 from Table 15					
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER			**Dominant**		**£73,573**
	Probabilistic results incorporating scenario numbers 1-5 from Table 15					
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER			**Dominant**		**£73,369**
A	Source of annual omalizumab cost: omalizumab MTA (probabilistic)					
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER			**Dominant**		**£72,965**
B	Using RRs for mOCS (probabilistic)					
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER			**£338,590***		**£104,129**
C	Random effects model for the NMA (probabilistic)					
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER			**Dominant**		**£73,855**
	Combination of scenario numbers A-C (probabilistic): ERG base case					
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER			**£43,084***		**£105,140**

*These ICERs lie in the South West quadrant and imply the costs saved per QALY lost with mepolizumab

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Mepolizumab for severe refractory eosinophilic asthma [ID798]

You are asked to check the ERG report from ScHARR to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, 17th Febraury** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

PRIORITY Issues 1- 12

Issue 1 Blood eosinophil thresholds for marker of response to Mepolizumab vs. diagnosis of SREA (Rational for ≥150/µL at screening threshold)

Description of problem	Description of proposed amendment	Justification for amendment
Throughout the ERG report, there is a misinterpretation of the blood eosinophil threshold that identifies increased response to add-on mepolizumab (i.e. ≥150/µL at screening). This is not a marker of diagnosis as suggested by the ERG (3.1 Population, page 23), however a marker of response to mepolizumab in patients already diagnosed with SREA (i.e. patient has been phenotyped and diagnosed as severe refractory eosinoplic asthmatic as highlighted in section 4.2.3.2 Subgroup analysis, page 64 of the ERG report, see justification column) where co-morbidities, acute exacerbations have been ruled out and patients have been optimised on standard of care (SOC, ie. step 4 or 5 of the BTS/SIGN guidelines). This is also supported by the phase III RCT inclusion criteria, which states that subjects had to have prior documentation or a high likelihood of eosinophilic asthma. Statistical justification for the sub-populations, Section 1.3, page 12: There has been a misinterpretation of the results and in fact Table 25 supports an eosinophil	We thus suggest a revision of the sections where the blood eosinophil threshold of ≥150/µL at screening is discussed to make the distinction that the GSK proposed eosinophil threshold of ≥150/µL at screening is a marker of response to add-on mepolizumab where a diagnosis of severe refractory eosinophilic asthma is already established. Please also see issue 2 which is relevant to the interpretation and conclusion of the blood eosinophil marker of response to mepolizumab. Reword sentence in section 1.3, page 12: ~~However, the results observed using a threshold of ≥300/µL in the previous 12 months (indicative of more severe asthma) were not intuitive and raise concerns over potential confounding factors.~~ To: Patients with ≥150/µL had a greater reduction in exacerbations for mepolizumab vs. placebo compared	We agree with the ERG's clinical experts that a historic marker is more valuable in diagnosis of severe eosinophilic patients (as correctly stated in section 3.1 Population, page 23, see ERG report). However, the blood eosinophil threshold identified in the CS is a marker of response to mepolizumab, as identified in DREAM (4.2.3.2 Subgroup analysis, page 64, see ERG report) in already diagnosed patients i.e. while ≥300/µL in the previous 12 months may be more valid in the diagnosis of severe eosinophilic asthma, once that diagnosis has been established ≥150/µL at screening is a valid marker of response to add-on mepolizumab in diagnosed patients on optimised standard of care (SoC). We agree with the clinical advisors that eosinophil levels can fluctuate. This supports the ≥150/µL at screening (instead of 'at some point in the previous year') which was taken after severe refractory eosinophilic asthma diagnosis has been confirmed at a time point where the patient is on optimised SoC and any acute disease states that could cause an artificially raised eosinophil count is excluded. This is in contrast to using a historic marker that was taken at any point in time in the last 12 months were the likelihood of eosinophil fluctuation being due to an acute exacerbation or unrelated factors is greater.

threshold of ≥150/µL at screening as a marker of response to add-on mepolizumab.	to patients with <150/µL. The results using a threshold of ≥300/µL in the previous 12 months (taken at any time point in the last 12 months) showed lesser reduction in exacerbations compared to patients with <300/µL (i.e. those patients that where included in MENSA study based on ≥150/µL at screening) who had greater reduction in exacerbations for mepolizumab vs. Placebo.	Reword sentence in section 1.3, page 12: The justification for the rewording is provided in the reworded paragraph.
Clinical validity of sub-populations, Section 1.3, page 13: It is not clear whether this statement is referring to accurate diagnosis or a marker of response in the diagnosed severe refractory eosinophilic asthmatic.	1.3, page 13: Add clarity on whether this comment was in regards to a valid marker for diagnosis or response to mepolizumab in an already diagnosed patient. Suggested wording: Clinical advisors to the ERG advised that a threshold of ≥300 cells/µL in the previous 12 months would be more appropriate <u>for the diagnosis of eosinophilic asthma</u> than ≥150/µL at screening, firstly because 150/µL is within the normal range and secondly because eosinophil levels can fluctuate.	1.3, page 13: It appears that the clinical advisors' advice was making a point regarding accurate diagnosis. By adding an explanation it will help to distinguish the importance of accurate diagnosis vs. utilising eosinophils as a marker of response to add-on mepolizumab.
Section 1.5, page 14 An invalid comparison is made between historic eosinophil counts.	Delete sentence in section 1.5, page 14 ~~The ERG has concerns regarding the threshold of blood eosinophil count of ≥150 cells/µL at screening included as a requirement in the GSK PP because it was unclear whether this would impact upon the effectiveness of mepolizumab in the medium and long-term, especially since a blood eosinophil count of ≥300 cells/µL in the previous year would by definition be greater than ≥150 cells/µL at some point in the previous year.~~	In regards to section 1.5, page 14, in addition to the argument made above that this is a marker of response to mepolizumab and not diagnosis, a comparison between ≥300 cells/µL in the previous year vs. ≥150 cells/µL at some point in the previous year is not applicable. The ≥150 cells/µL eosinophil count was taken at screening in a controlled environment and no data of for a historic ≥150 cells/µL is available. In addition, as discussed before ≥150 cells/µL at screening is a better predictor of response to mepolizumab compared to ≥300 cells/µL in last 12 month.
2.1 Critique of manufacturer's description of underlying health problem, Severe eosinophilic asthma, page 19: This section does not clearly distinguish between eosinophilic asthma	Add sentence at the end of paragraph in section 2.1, page 19: There is no national or international	

diagnosis and identifying an eosinophil marker of response in the already diagnosed patient. 3.1 Population, page 27 and 4.2.3.2 Subgroup analysis, page 66: Again it is important to distinguish between eosinophilic asthma diagnosis and identifying an eosinophil marker of response to mepolizumab in the already diagnosed patient. 4.2.3.2 Subgroup analyses, Page 65:	consensus on how to interpret such tests; however, clinical advisors to the ERG stated that a level of ≥300 cells/μL in the previous 12 months is a commonly used cut-off. The CS states "Eosinophilic asthma inflammation can be measured in both blood and sputum, but recent studies have confirmed that late-onset severe refractory eosinophilic asthma can be reliably characterised by establishing blood eosinophil thresholds in the presence of high-dose ICS in a poorly controlled exacerbating phenotype" (p 25-26), and references two articles19, 20 to support this statement, both of which are re-analyses of the phase IIb trial, "Dose Ranging Efficacy And safety with Mepolizumab in severe asthma" (DREAM), which forms part of this submission. The ERG concludes that the use of blood eosinophilia to identify eosinophilic asthmatics appears to be a clinically relevant approach, but that the criteria that should be used to diagnose eosinophilic disease are unclear and of uncertain accuracy. The CS assumes that all patients have been diagnosed as severe refractory eosinophilic asthmatic and are optimized on SoC before being considered eligible for add-on mepolizumab therapy. Thus the CS used a blood eosinophil threshold of ≥150 cells/μL at screening as a marker of increased response to add-on mepolizumab therapy (not as diagnostic marker). Section 3.1, page 27: Delete section of text: Subgroup analyses indicate that a blood eosinophil threshold of ≥150/μL at screening provides a greater reduction in exacerbation rate than a threshold of ≥300/μL in the previous 12 months. ~~However, it is not clear why this should be the case. Clinical advisors to the ERG advised that a blood eosinophil threshold of 300/μL in the previous 12 months would appear more appropriate than 150/μL at screening, because 150 cells/μL was a relatively low count within the~~	In regards to section 2.1, page 19 it is important to highlight again that a clear distinction should be made between diagnosis of severe eosinophilic asthma and identifying a marker of response to add-on mepolizumab in the already diagnosed patient. Section 3.1, page 27 and section 4.2.3.2 Subgroup analysis, page 66: The highlighted text discusses a valid eosinophil count for diagnosis. The clinicians' argument is that historic eosinophil counts are more valuable in diagnosis. We agree with the clinical advisors in section 3.1, page 23. It is important to emphasize again that the ≥150/μL at screening threshold is not a marker for diagnosis. It is a marker that aims to identify already diagnosed patients that have additional benefit from add-on mepolizumab therapy. Although 150 cells/ul is within the normal range and

Figure 1 looking at predicted rate of exacerbations by baseline eosinophil count has been misinterpreted. 4.2.3.2 Subgroup analyses, Page 66: Suggest rewording of sentence to ensure the statement reflects a balanced view of the entire data presented in table 24.	~~normal range, and because eosinophil levels can fluctuate.~~ 4.2.3.2 Subgroup analysis, page 66: This compares two different options for a blood eosinophil threshold: ≥150/μL at screening, or ≥300/μL in the previous 12 months~~. Clinical advisors to the ERG advised that a threshold of 300 cells/μL would appear more appropriate since 150 cells/μL was a relatively low count which was within the normal range, and that a threshold observed anytime in the previous 12 months would seem more appropriate than one observed exactly at the point of screening since eosinophil level can fluctuate.~~ 4.2.3.2 Subgroup analyses, Page 65: Suggested following changes: The ERG considers that the justification of the derived threshold should be interpreted with caution. Figure 1 suggests that, for the placebo group in DREAM, the predicted rate of exacerbations increases notably as baseline blood eosinophils increases, whilst for the mepolizumab group, the predicted rate of exacerbations decreases. This phenomenon is also seen in the MENSA trial. ~~No clinical justification is provided for why, in the treatment group, patients with higher baseline blood eosinophils (indicative of more severe asthma) would have a lower predicted rate of exacerbations~~ Eosinophilic asthmatics have a higher risk of exacerbations as this risk increases with increased levels of inflammation (i.e. an increased eosinophil count). In addition, the phase IIb/III RCT results provided evidence that mepolizumab's efficacy increases as the baseline eosinophil level increases (Figure 2 & 3). Thus, as expected in the placebo arm (i.e. patients on SoC not treated with mepolizumab) the disease severity (predicted rate of exacerbations per year) increases as the eosinophil blood count increases, while patients with an increased eosinophil count show an increased response to add-	we accept that these levels can fluctuate we have demonstrated that this criterion does identify patients with an enhanced capacity to benefit and hence provide a more clinically and cost effective use of NHS resources. 4.2.3.2 Subgroup analyses, Page 65: This ensures a factually correct interpretation of figure 1 in relation to a blood eosinophil level as marker of response and includes correct Rate Ratios (95% CIs) of Clinically Significant Exacerbations at Thresholds of Baseline Blood Eosinophils at 150/μL, 300/μL and 500/μL.

	on mepolizumab therapy as the eosinophil count increases (i.e. a reduction in the predicted rate of exacerbations per year can be seen). Figure 1 ~~does not~~ conveys ~~the uncertainty in~~ the relationship between baseline blood eosinophils and rate of exacerbations, ~~or a confidence interval~~ associated with this clinically significant 30% reduction. ~~Whilst~~ The interaction term was found to be statistically significant (p=0.0001). ~~), the main effect of the blood eosinophils was not found to be statistically significant at the~~ ~~5% level and so there is likely to be considerable uncertainty associated with the illustrated predicted rates..~~ In DREAM the rate ratios for 150/µL, 300/µL and 500/µL were 0.7 (95% CI 0.53, 0.93), 0.52 (0.41, 0.65) and 0.42 (0.32, 0.54), respectively. While, in MENSA the rate ratios were 0.61 (0.45, 0.82), 0.49 (0.38, 0.63) and 0.42 (0.31, 0.55).While the main effect of the blood eosinophils was not found to be statistically significant at the 5% level for DREAM, in MENSA it was significant (p=0.002). 4.2.3.2 Subgroup analyses, Page 66: Using data from DREAM (n=286, 46% of total) and MENSA (n=245, 43% of total), for patients with 2 exacerbations a threshold of between 350 and 400 cells/ µL and between 100 and 150 cells/ µL, respectively would be required to achieve the specified reduction in rate. For patients with ≥4 exacerbations (representative of the GSK PP) the reported threshold is <50 cells/ µL in DREAM and between 50 and 100 cells/ µL in MENSA. .	4.2.3.2 Subgroup analyses, Page 65: This will allow a fair interpretation of table 24 in relation to a blood eosinophil level as marker of response to mepolizumab.

Issue 2 Interpretation of ≥300/µL in the previous 12 months blood eosinophil count

Description of problem	Description of proposed amendment	Justification for amendment
1.2 Subgroup analyses, page 10 and 4.2.3.1 Clinical effectiveness in ITT and GSK populations, Baseline blood eosinophil threshold, page 67: Table 25: analysis of rate of clinically significant exacerbations by blood eosinophil criteria has been misinterpreted.	1.2 Subgroup analyses, page 10 - Suggest rewording: Patients with ≥150/µL at screening had a greater reduction in exacerbations for mepolizumab vs. placebo than patients with <150/µL; ~~this was not the case when the population was subgrouped using a threshold of ≥300/µL in the previous 12 months~~ This was not the case when the population was subgrouped using a threshold of ≥300/µL in the previous 12 months. This reinforces that a marker of ≥300/µL in the previous 12 months is not a robust marker of response to mepolizumab. Patients with <300/µL showed a greater reduction in exacerbations; these patients entered the MENSA trial by the ≥150/µL at screening inclusion criterion. This supports the ≥150/µL at screening threshold as a marker of response to mepolizumab. 4.2.3.1 Clinical effectiveness, page 67 - Suggested change: Delete text: ~~However, the results observed for subgroups based on a threshold of ≥300/µL in the previous 12 months were not intuitive for the following two reasons:~~ ~~1) Exacerbation rates in the placebo groups were lower for patients with ≥300/µL in the previous 12 months compared with patients with <300/µL (1.64 vs. 1.89), and~~ ~~2) Patients with ≥300/µL in the previous 12 months had a smaller reduction in exacerbations for mepolizumab vs. placebo (RR=0.69 and 0.57) than patients with <300/µL (RR=0.27 and 0.27), which is not intuitive.~~ and replace with: Moreover, the blood eosinophil count of ≥150/µL at screening is supported by the subgroups based on a threshold of ≥300/µL in the previous 12 months. 1) Exacerbation rates in the placebo	1.2 Subgroup analyses, page 10 - Suggest rewording: This ensures a factually correct interpretation of the ≥300/µL in the previous 12 months subgroup results (with reference to table 25, section 4.2.3). 4.2.3.1 Clinical effectiveness, page 67: We suggest this rewording as the results in table 25, page 67 are intuitive and align with ≥150/µL at screening as valid blood eosinophil marker of response. Patients in MENSA entered the trial by two eosinophil inclusion criteria (1) ≥150/µL at screening or (2) ≥300/µL in the previous 12 months. Thus patients that had a blood eosinophil count of <300/µL in the previous 12 months entered the trial by fulfilling the ≥150/µL at screening inclusion criterion. The CS demonstrates that ≥150/µL at screening is a more robust marker of treatment response in the already diagnosed severe eosinophilic asthma patient, in whom co-morbidities are excluded and acute disease states are excluded and patients have been optimised on SOC. To point 1) this could explains why patients with <300/µL in the previous 12

	groups were lower for patients with ≥300/μL in the previous 12 months compared with patients with <300/μL, i.e. patient that fulfilled the ≥150/μL at screening inclusion criterion in MENSA (1.64 vs. 1.89), and 2) Patients with ≥300/μL in the previous 12 months had a smaller reduction in exacerbations for mepolizumab vs. placebo (RR=0.69 and 0.57) than patients with <300/μL, i.e. those patients that were included in MENSA based on an eosinophil count of ≥150/μL at screening (RR=0.27 and 0.27), which is in support of the ≥150/μL at screening threshold. This is consistent with table 20 (page 78) in the CS, which confirms ≥150/μL at screening as a robust marker of response to mepolizumab (RR=0.28 and 0.26) compared to ≥300/μL in the previous 12 months (RR=1.06 and 0.82).	months (i.e patients fulfilling the inclusion criterion of ≥150/μL at screening) show a greater rate of exacerbations. To point 2) based on the argument for ≥150/μL eosinophil blood marker at screening, explains why patients with <300/μL in the previous 12 months (i.e patients fulfilling the inclusion criterion of ≥150/μL at screening) show a greater reduction in rate of exacerbations for mepolizumab vs. placebo.

Issue 3 Combining Roberts and Watson

Description of problem	**Description of proposed amendment**	**Justification for amendment**
P128. The ERG report refers to the two exploratory analyses which were undertaken during the clarification stage, to try to obtain some differentiation of asthma mortality by age group. In our clarification response we cautioned on the reliability of the exploratory analyses. This is not mentioned by the ERG in its report.	Please add in some text putting these analyses into context: Based on the information provided in the Watson et al publication, no further stratification can be made in age group ≥45, hence why the risk of mortality was grouped in the analysis as it is, when the analyses are based on the Watson data. In its clarification response, exploratory analyses were conducted by the company to explore differentiate mortality risk by increasing age, however the company explained that it is not possible to obtain an accurate risk of mortality for the age group 45-54, 55-64 and 65 years and above, using the data published by Watson et al, and so these exploratory analyses have not been validiated and should be interpreted with caution.	To put these additional analyses into context; to clearly explain that these results were exploratory only, that they have limited validity and should be interpreted with caution.

Issue 4 Using COSMOS data as exacerbation rates for those meeting the continuation criterion

Description of problem	Description of proposed amendment	Justification for amendment
Using a RR of 0.9 from COSMOS for those meeting the continuation criterion is not appropriate. This is because COSMOS also included people who did not meet the continuation criterion but remained on mepolizumab, as well as those who were previously on the SoC arm and so have received mepolizumab for a shorter period of time. The population would therefore include patients who meet and do not meet the continuation criterion. Thus this value is likely to overestimate the RR of exacerbation rate for people on mepolizumab post continuation.	The values applied are not accurate rates for people post continuation, and so the applicability of this analysis should be cautioned against and removed from the list of the proposed scenario analyses.	To ensure that decision making is carried out based on the most appropriate and accurate information.

Issue 5 Like omalizumab approach to mortality

Description of problem	Description of proposed amendment	Justification for amendment
P128. The ERG also notes that the type of exacerbations considered in the omalizumab MTA within the Single Technology Appraisal of mepolizumab differed and thus so did their frequency in the SoC treatment arm (annual rates of 0.885 and 1.744 respectively used in the ITT populations for the omalizumab and mepolizumab appraisals respectively). Therefore the ERG notes that using the same approach to model asthma-related mortality as in the omalizumab MTA was of limited validity. Whilst the approaches used to categorise exacerbations are indeed different, this does not provide a reason to conclude that using the approach to model asthma-	The ICERs corresponding to applying the like omalizumab approach on mortality should be presented and discussed. E.g. you could add in text along the following lines: An approximate replication of the approach that was settled on for representing mortality within NICE MTA278, as set out in the Final Appraisal Document, was conducted by the company. This was to use the midpoint mortality estimates between Watson et al and de Vries et al., increased by 15% to account for very severe disease. This approach was used in the additional analyses submitted by the manufacturer after the second committee meeting, was ratified by the assessment group, and formed the basis of the assumptions on which the most plausible ICER was calculated. Applying the same assumption to the base case, reduced the ICER from £19,526 to £15,645 in the GSK PP and from £15,394 to £13,854 in the GSK PP excl. stable	For consistency across decisions and appraisals.

related mortality is of limited validity. Even if this ERG does not agree with the approach used in the appraisal of omalizumab to model asthma related mortality, for transparency it would be useful to present and explain the effect on the ICER of applying the same model inputs for mortality, as this was the approach which was accepted by the committee in order to obtain the most plausible ICER in the omalizumab HTA.	mOCS.	

Issue 6 Data using broader population would produce a 'more plausible ICER'

Description of problem	Description of proposed amendment	Justification for amendment
P17. Using data from the ITT population with ≥4 exacerbations, rather than with an additional criterion of having ≥150 cells/μL at screening, would produce a more plausible ICER for mepolizumab versus SoC.	Using data from the ITT population with ≥4 exacerbations, rather than with an additional criterion of having ≥150 cells/μL at screening, would produce an ICER in this additional population ~~more plausible ICER~~ for mepolizumab versus SoC.	The GSK pp identifies a specific population that is clinically relevant and is cost effective. The ICERs generated for the GSK pp are appropriate and sound for this restricted population. It is factually inaccurate to state that running analyses in a broader population would give more plausible ICERs. They would indeed give different ICERs because we would be looking at a different population.

Issue 7 mOCS as a relevant comparator

Description of problem	Description of proposed amendment	Justification for amendment
There are 3 separate parts relating to this issue: 1) P129. The ERG believes that mOCS is a relevant comparator for the GSK PP We do not believe that mOCS in its own right is a relevant comparator for the GSK PP.	Remove all discussion and text relating to mOCS being a relevant treatment option in its own right.	mOCS as a relevant comparator was discussed within the scoping workshop and was dismissed, thus it was not included in the scope. However mOCS is allowed as part of SoC (and was permitted in our clinical studies) and so in effect the use of mOCS is considered as part of SoC.

2) P14 The addition of mOCS in patients who are not contraindicated would likely reduce the average number of exacerbations and therefore reduce the relative benefit of mepolizumab. It is inaccurate to say that the addition of mOCS in patients who are not contraindicated would likely reduce the average number of exacerbations and therefore reduce the relative benefit of mepolizumab, because those eligible for receiving mOCS were already receiving mOCS throughout the trial period in MENSA and in DREAM, thus this effect is already captured within the trial results. 3) P14. The SIRIUS trial could have provided a better insight for this comparison, but the analysis using the data from SIRIUS was subject to a high degree of uncertainty due to the small size of the GSK PP in this trial. It is inaccurate to say that the SIRIUS trial could have provided a better insight for comparison.	Remove text: ~~The addition of mOCS in patients who are not contraindicated would likely reduce the average number of exacerbations and therefore reduce the relative benefit of mepolizumab.~~ Remove text~~: P14. The SIRIUS trial could have provided a better insight for this comparison, but the analysis using the data from SIRIUS was subject to a high degree of uncertainty due to the small size of the GSK PP in this trial.~~	25% of MENSA and 31% of DREAM patients were on mOCS, as part of optimised treatment in SoC (as well as on mepo), and so the economic assessment of mepolizumab compared with SoC, is on top of mOCS, for those people in whom mOCS is appropriate. The SIRIUS trial was designed to assess the mOCS sparing effect of mepolizumab, 66 patients received treatment with mepolizumab arm and assessed after 24 weeks. SIRIUS was not designed, nor powered to assess the effect of treatment on exacerbations.

Issue 8 SIRIUS calculations

Description of problem	Description of proposed amendment	Justification for amendment
1. Table 73, Result of the exploratory analyses based on SIRIUS, the values don't seem to add up. For the ITT population, for both the pop specific utilitites and	Please check the calculations in this section and then, if appropriate, revise relevant sections of the report with the correct values.	To ensure the values presented are corrected.

the ITT utilities, the values reported are the same, and using these values, I calculate an ICER of £60,414 (rather than £84,700 as reported). Further, in the GSK PP analyses, the pop specific utilities, weget an ICER of -£42,123 (compared with £147,637 in the table). 2. The objective of SIRIUS was to look at how much of a reduction in mOCS use could be achieved, whilst maintaining asthma control. To therefore conduct and present the analyses presented in table 73 are of limited value, and could be misinterpreted. .	Please consider adding into the report, something to the following effect: The SIRIUS study was not powered to detect changes in exacerbation rates. The SIRIUS trial was designed to assess the mOCS sparing effect of mepolizumab, 66 patients received treatment with mepolizumab arm and were assessed after 24 weeks. SIRIUS was not designed, nor powered to assess the effect of treatment on exacerbations. The objective of the study was to look at how much of a reduction in mOCS use could be achieved, whilst maintaining asthma control.	To help aid the reader contextualise these results.

Issue 9 Omalizumab analyses and combined ICER

Description of problem	**Description of proposed amendment**	**Justification for amendment**
P17, p153 and 154 P142, 143 – ERG's alternative assumptions. Nine issues with this: 1. In our check, we obtained different values for your omalizumab comparison: if we use the values in table 74, Results of exploratory analyses ERG omalizumab, the ICER is £714. If simplistically we assume there are no interactions between the scenarios and just take the mean of your scenarios A-C to get costs and effects, then the combined ICER is £-211,778 (i.e. dominant).Neither of which are near £43,084. 2. The report states that the	1. Please check the calculations in this section and then, if appropriate, revise relevant sections of the report with the correct values. 2. For accuracy, please stick to comparing mepo with oma in that order (rather than	To ensure the values presented are corrected. To help aid the reader. To ensure that the reader understands what it means for an ICER to be in the south west quadrant. To ensure that the analyses are presented using appropriate inputs.

ICER for omalizumab versus mepolizumab was approximately £43,000 per QALY gained (and in the table it is mepo vs oma). We would expect to see mepo vs oma in all cases. 3. The ICER that is stated of £43,000 is in the SW quadrant and this is not clear to the reader, who may think that this is not cost effective, when actually in this quadrant, a value greater than the threshold means that a treatment is cost effective. 4. It is not clear in the report (p 17 and p153) that the ICER of £43,000 per QALY gained has been derived from two dominant ICERs and one ICER of £338,590 (which as above shows mepo to be strongly cost effective). At the moment it could be interpreted as not being cost effective and that is not the case. 5. You present some additional mepo vs SoC analyses that you have done using data from the NMA, but don't mention this in the results section of the text, or provide context about it, which could cause confusion to the reader. 6. We expect similar methods and text have been used in the confidential appendix, and so we encourage the ERG to apply the same amends to that appendix as for this issue. 7. Appropriateness of using the assumed annual cost of omalizumab reported in the MTA compared to that reported in a study conducted by GSK to estimate the current cost of omalizumab in clinical practice.(p142,p122).	omalizumab compared with mepolizumab) 3. Should the updated calculations give an ICER in the SW quandrant, please add some text around this to aid the reader in their interpretation. i.e. ICERs in the SW quadrant that are greater (rather than below (as in the NE quadrant)) than the threshold value are generally regarded as being cost effective. It might also be worth expanding your footnote in table 73 to incorporate this, given that the £338,590 ICER is there. 4. Once the recalculated combined ICER has been obtained, it should be made clear to the reader that is formed of two dominant strategies and one very cost effective scenario (albeit in the SW quadrant). 5. Either remove this column altogether, as it is could lead to some confusion, else provide a clear description of what it relates to, which population etc and an explanation of what relevance it has to the decision problem. 6. Please check your calculations in the appendix as per the reasoning above and apply the changes mentioned in the appendix. 7. Consider adding in the following information: • In the GSK study, the costs estimated for the year of the MTA were very similar to that assumed in the MTA (£7959 in 2011 vs £8,056 assumed by	It is a reasonable assumption that the cost of omalizumab as utilised in the NHS currently is significantly higher than that used for the omalizumab MTA, and our data show this to be the case. An analysis which is based on an unrealistic assessment of costs to the NHS purely on an unjustifiable concern on relative effectiveness will not accurately reflect the opportunity cost to the NHS of using mepolizumab vs

Whilst the ERG does not dispute the validity of the new values it could add two additional piece of information that support this conclusion. 8. The ERG comments that it is unclear whether this change in the dosing has any impact on the effectiveness of omalizumab. In the SmPC for Omalizumab it is clear that dosing depends purely on weight and baseline IgE levels and there is no reference to any impact on effectiveness depending on dose. We would therefore argue that the evidence suggests that there is no reason to expect that an increase in cost would result in any changes in effectiveness. 9. Alternative assumption B: mOCS use is part of treatment in the patient population in whom mepolizumab is proposed to be used in. It is not clear why the ERG thinks that we should restrict the use of mepolizumab compared with omalizumab to people who are on mOCS only. This would not be in line with our marketing authorisation, nor our proposed population. Thus to use a value for the RR of 0.77 rather than 0.316 is inaccurate and inappropriate.	NICE) supporting the validity of the methodology used for the research. • In a recent review of omalizumab by the NCPE (October 2015), a real world average cost of omalizumab was found to be £11,723. This is similar to that obtained in the GSK study of £11,370. 8. Consider removing this assumption, else add in some additional text, to the following effect: The SmPC for omalizumab dosing depends purely on weight and baseline IgE levels. There is no reference to an impact on effectiveness depending on dose. 9. Remove application of RR of 0.77 rather than 0.316 in alternative assumption B.	omalizumab in patients eligible for both medicines. To ensure mepolizumab is assessed in line with its marketing authorisation and in line with proposed populations.

Issue 10 Severe refractory asthma definition

Description of problem	Description of proposed amendment	Justification for amendment
2.1 Critique of manufacturer's description of underlying health problem, page 18 The definition of severe refractory asthma is not stated in completeness.	2.1 Critique of manufacturer's description of underlying health problem, page 18 – suggest rewording: The term "severe refractory asthma" is used in the license and the summary of product characteristics (SmPC) for mepolizumab. According to definitions	2.1 Critique of manufacturer's description of underlying health problem, page 18 : In addition to ATS/ERS and BTS/SIGN guidance, an international consensus on the definition of severe

	from the ATS/ERS, the BTS/SIGN guidelines and the U-BIOPRED Consortium (Ref in justification column) these are patients who remain uncontrolled despite treatment with high dose ICS plus a second controller ~~and/or systemic corticosteroids.~~or can only maintain adequate control when taking systemic corticosteroids and are thereby at risk of serious adverse effects of treatment'. In addition, patients' asthma diagnosis should be confirmed, alternative diagnoses have been excluded, comorbidities have been treated, trigger factors have been removed (if possible) and compliance with treatment has been confirmed.	refractory asthma has been agreed. This should be reflected in the ERG report. The consensus has been published in 2011 by Bel et al. (Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax 2011;66:910): 'The term 'severe refractory asthma' should be reserved for patients with asthma in whom alternative diagnoses have been excluded, comorbidities have been treated, trigger factors have been removed (if possible) and compliance with treatment has been checked, but still have poor asthma control or frequent (≥2) severe exacerbations per year despite the prescription of high-intensity treatment or can only maintain adequate control when taking systemic corticosteroids and are thereby at risk of serious adverse effects of treatment. For this definition, poor asthma control is defined according to Juniper et al as a score of ≥1.5 by the 7-item Asthma Control Questionnaire or an equivalent score by any other standardised asthma control questionnaire. High-intensity treatment in adults is defined as ≥1000 mg/day fluticasone equivalent and/ or daily oral corticosteroids combined with long-acting b2 agonists or any other controller medication.'

Issue 11 Continuation criteria

Description of problem	Description of proposed amendment	Justification for amendment
P15. The ERG has concerns regarding the continuation criteria defined for mepolizumab...According to these, all patients who did not	Amend text to read something along the lines of: This implies that a proportion of patients would remain on	Patients could be receiving benefit in the form of reduced OCS exposure or symptomatic improvement. That is the reason we have

experience a worsening in exacerbation rates would receive mepolizumab. This implies that a proportion of patients would remain on mepolizumab despite experiencing no improvement. This statement does not factor in the multifaceted nature of treatment with mepolizumab to the patient.	mepolizumab despite experiencing no numerical improvement in exacerbations, however patients could be receiving benefit in the form of reduced OCS exposure or symptomatic improvement.	left in patients whose exacerbation remained the same.

Issue 12 OCS sparing comparison to omalizumab

Description of problem	Description of proposed amendment	Justification for amendment
1.6.2 Weaknesses and areas of uncertainty, page 16 and 5.2.11.3 Scenario analysis: OCS sparing, page 126: Inappropriate comparison of two endpoints from different clinical trials These data are obtained from different sources and are not comparable in this way. As we understand it, It is not the case that 41.9% of patients in EXALT stop OCS. Only 22% of patients are on OCS patients at baseline. Of these, 76.8% are responders and 41.9% of those patients stop OCS. Which means 0.22*0.768*0.419 = 0.0708. So it is about 7.1% of Xolair patients who stop OCS vs. 14.5% from SIRIUS. Further the OCS sparing is reported as being from EXALT but this result is not reported in the trial publication (Bousquet 2011).	Delete sentence in section 1.6.2, page 16: ~~However, it is noted that the cessation of OCS use was greater for omalizumab than for mepolizumab, as 41.9% of patients discontinued mOCS on omalizumab compared with 14.5% on mepolizumab~~ Delete sentence in section 5.2.11.3, page 126: ~~The ERG notes that data relating to the proportion of patients discontinuing OCS are available in the Assessment Group's report for the omalizumab MTA and are markedly different from those for mepolizumab: 14.5% of patients discontinued OCS treatment in SIRIUS compared with 41.9% of omalizumab responders.~~	For reasons stated below we feel that a direct comparison of OCS dose reduction with mepolizumab vs. omalizumab is not appropriate.Suggest deletion of the highlighted sentences as it is not clear whether a direct comparison of these percentages is valid. While the mepolizumab data is from a double blinded RCT (SIRIUS) the omalizumab data referred to in the ERG report is from an open label study (EXALT), where OCS sparing was an exploratory endpoint. In addition, it is not made clear if the patient demographics were comparable in these studies and whether patients were optimized on OCS therapy before assessment of OCS reduction. Furthermore, the Assessment Group report from the omalizumab MTA referred to clearly states that 'Evidence that omalizumab treatment reduced OCS use was limited: the OCS maintenance subgroup of EXALT showed statistically significant benefits; this was not found in a subgroup of one other RCT in controlled patients.' The Assessment Group highlights several other limitations with the steroid sparing evidence for omalizumab in their report that are not reflected by the ERG. Ten uncontrolled observational studies reported data on oral corticosteroid use after

		omalizumab treatment. For adults on maintenance oral corticosteroids, the proportion of patients reducing or stopping oral corticosteroids ranged from 25.9% to 71.2% after omalizumab treatment. The most recent evidence for OCS reduction with Omalizumab therapy comes from a retrospective observational study, APEX I and a prospective observational study, APEX II. Both of these studies are inappropriate for comparison to robust RCT results in SIRIUS, where patients were optimised on the lowest OCS dose that achieved asthma control before assessment of OCS reduction. In APEX I the mean daily OCS dose (on OCS-treated days) decreased by 5.5 mg (25.6%), from 21.4 mg pre-omalizumab to 15.9 mg post- omalizumab (p <0.001). In APEX II the mean daily OCS dose significantly decreased by 16% from 10.3 mg/day (±7.1) to 8.7 mg/day (±8.6) (p <0.001). Thus, a direct comparison of the discontinuation percentages from the open label EXALT study and SIRIUS does not give a fair representation of the totality of available evidence and is arguably misleading.

LOWER PRIORITY Issues 13 to 33

Issue 13 SGRQ data in Summary

Description of problem	Description of proposed amendment	Justification for amendment
Section 1.2, page 10 Factually inaccurate SGRQ and ACQ data presented in section 1.2	Amend text to: In terms of quality of life, differences on the St. George's Respiratory Questionnaire (SGRQ) for MENSA and SIRIUS for mepolizumab vs. placebo ranged from 5 to ~~13~~ 12.8 units (p<0.001 for meta-analysed results), in all sub-populations except	To ensure results stated are presented factually accurate.

	in stable mOCS patients where the difference was 4.3 (p=0.106). All subgroups achieved the minimal clinically important difference [MCID] of 4 units. Differences on the Asthma Control Questionnaire (ACQ) meta-analysed across MENSA and DREAM ranged from -0.334 to -0.78 (p<0.001 for all) across all sub-populations except in stable mOCS patients where the difference ranged between 0.3 (p=0.144) and 0.43 (p=0.007) (MCID 0.5 units).	

Issue 14 Exacerbation rates for patients meeting the continuation criteria

Description of problem	Description of proposed amendment	Justification for amendment
Section 1.5, Page 15, The ERG report states that: these rates were measured in the MENSA trial shortly after the beginning of treatment, based on a 16-week time span and therefore might not be representative of the long-term effectiveness of mepolizumab Also on p111 and 129 The statement is not clear on how the rate of exacerbations in subjects continuing treatment were calculated, and also is factually inaccurate to say that these rates were measured 'shortly after the beginning of treatment'.	Page 15: ~~these rates were measured in the MENSA trial shortly after the beginning of treatment, based on a 16-week time span and therefore might not be representative of the long-term effectiveness of mepolizumab~~ Consider changing to: Due to constraint of available data, these rates were measured in the MENSA trial, 16 weeks after the beginning of treatment, where subjects were split according to the continuation rule, and were based on 16 weeks of follow-up after this (week 16-32). This might not be representative of the long-term effectiveness of mepolizumab. P111.Thirdly, given that the exacerbation rate is measured~~shortly after treatment initiation~~, from 16 weeks to the end of the 32 week study this may not be representative of its long-term effectiveness.	In order to provide a reliable estimate of the exacerbation rate in subjects meeting the continuation rule, sufficient follow-up is required prior to and after the continuation rule assessment. Therefore, the rates were measured using data on exacerbations from week 16 to end of study (week 32). The amendment proposed provides clarification to the statement.

Issue 15 Exacerbation rate of patients returning to SoC arm

Description of problem	Description of proposed amendment	Justification for amendment
Section 5.2.6, Page 111. The ERG states that 'Patients not meeting the	Patients not meeting the continuation criteria at continuation assessment (1 year in the base case) are taken off mepolizumab treatment and are	Given that the exacerbation rates used in the model are for specific populations, it is

continuation criteria at continuation assessment (1 year in the base case) are taken off mepolizumab treatment and are subsequently assumed to experience the same exacerbation rate as those patients in the SoC group. The ERG notes that this assumption is likely to underestimate the exacerbation rate of this subgroup of patients because these were the more severe patients and are likely to have higher rates of exacerbations'. We do not believe that this would be the case for the reasons stated in the justification column..	subsequently assumed to experience the same exacerbation rate as those patients in the SoC group. The ERG notes that ~~this assumption is likely to underestimate the exacerbation rate of~~ this subgroup of patients ~~because these were the more severe patients and~~ are likely to have higher rates of exacerbations than on mepolizumab, and this is captured in the modelling via the higher exacerbation rate in the SoC comparison compared with the mepolizumab comparison.	unclear why the ERG is of the opinion that those people who don't meet the continuation crierion would be more severe patients and are thus likely to have a higher rate of exacerbations than modelled for SoC. The continuation criterion is a marker of response/non response not severity of disease. They are likely to have a higher rate of exacerbations: the higher annual rate for SoC in the model accounts for a higher annual exacerbation rate in this group, and so is not an underestimation.

Issue 16 Categorisation of deaths as per NRAD

Description of problem	Description of proposed amendment	Justification for amendment
Section 5.2.7, Page 114. The ERG notes that should any of the deaths in Watson *et al*. be assignable to the 'hospital, pre-hospital arrest' category, then the number of deaths due to asthma exacerbations would be overestimated. None of the deaths in Watson were assigned to the hospital, pre hospital arrest category (these were considered to relate to ED), thus this statement is not relevant.	This text should be deleted: ~~The ERG notes that should any of the deaths in Watson *et al*. be assignable to the 'hospital, pre-hospital arrest' category, then the number of deaths due to asthma exacerbations would be overestimated.~~	None of the deaths in Watson were assigned to the hospital, pre hospital arrest category (these were considered to relate to ED), thus it is not relevant, but also may cast doubt in the mind of the reader without cause.

Issue 17 Length of an exacerbation taken from MENSA

Description of problem	Description of proposed amendment	Justification for amendment
Section 5.2.11.2, Page 125. When the source for the length of utility decrement caused by exacerbations was taken from MENSA, rather using the four-week assumption based on Lloyd *et al*.,[51] there was a small	Please add in detail to the ERG report about the lengths of utility decrement that were used from MENSA in this scenario.	For completeness and to aid comprehension and interpretation of the results.

increase in the ICER. Whilst not a factual inaccuracy as such, it would be helpful to the reader if the values which were used in this assumption were clearly stated in the ERG report, thus they can be discussed in an open and transparent way.		

Issue 18 Results using the data from the meta-analysis on DREAM and MENSA

Description of problem	Description of proposed amendment	Justification for amendment
Section 5.2.11.4, Page 129. The ERG also requested a scenario analysis based on the exacerbation rates and utilities recorded in the DREAM trial and analyses where exacerbation rates were calculated through a meta-analysis of data gathered in MENSA and DREAM, both using EQ-5D utilities (DREAM) and the SGRQ-mapped utilities (MENSA). There is no mention in this statement that the results of this request were provided to the ERG within the company response, so please add this in.	Page 129. The ERG also requested a scenario analysis based on the exacerbation rates and utilities recorded in the DREAM trial and analyses where exacerbation rates were calculated through a meta-analysis of data gathered in MENSA and DREAM, both using EQ-5D utilities (DREAM) and the SGRQ-mapped utilities (MENSA). The results of this request were provided to the ERG within the company response.	To explain that these data were not only requested by the ERG, but were also provided.

Issue 19 Step 4/step 5

Description of problem	Description of proposed amendment	Justification for amendment
Section 2.2, page 21 The ERG report states: In the clinical care section of the CS (Section 3.3 p27), the company identifies patients at BTS/SIGN[4] Step 5 as the focus of the appraisal, although p11 of the CS states that *"people with severe refractory asthma are typically termed Step 4 or Step 5 patients"*. However, the NICE scope considers the relevant	In the clinical care section of the CS (Section 3.3 p27), the company identifies patients at BTS/SIGN[4] Step 4 and 5 as the focus of the appraisal, ~~although~~ and p11 of the CS states that *"people with severe refractory asthma are typically termed Step 4 or Step 5 patients"*. ~~However, t~~he NICE scope considers the relevant comparators to be care according to Step 4 or Step 5 of the BTS/SIGN guidelines.[4] This corresponds to the steps that would fall within the ATS/ERS definition of severe asthma	Mepolizumab is licensed for adults with severe refractory eosinophilic asthma. This includes uncontrolled step 4 patients (i.e. on high dose ICS + additional controllers) By being uncontrolled on step 4 patient classify for step 5 treatment, which includes therapies such as mOCS and biologics [e.g. mepolizumab]).

comparators to be care according to Step 4 or Step 5 of the BTS/SIGN guidelines.[4] This corresponds to the steps that would fall within the ATS/ERS definition of severe asthma provided in Section 2.1, and is consistent with the definition used in the NRAD report (p31).[22] As such, the ERG believes that the company's focus is too narrow and that both Steps 4 and 5 should be considered to be relevant. We acknowledge that the diagram in Figure 2 of the CS is not very clear, but it does show that we are looking at step 4patients , moving into step 5, and also step 5 in their own right. We therefore think that this statement in the report is incorrect.	provided in Section 2.1, and is consistent with the definition used in the NRAD report (p31).[22] As such, the ERG believes that the company's focus is ~~too narrow and that both Steps 4 and 5 should be considered to be~~ relevant.	The company submission does cover both step 4 and 5 patients.

Issue 20 Clinical trial evidence

Description of problem	Description of proposed amendment	Justification for amendment
3.1.2 GlaxoSmithKline (GSK) clinical trial evidence (ITT population), page 24. Factual inaccuracies of CSRs:	Two of the trials (DREAM and MENSA) also use a criterion of ≥2 asthma exacerbations requiring treatment with systemic corticosteroids in the previous 12 months, '~~which is presumably a measure of loss of control~~' to: which has been accepted as a measure of loss of control by the international consensus statement from the Innovative Medicine Initiative (Bel et al. 2011). ~~It is unclear if patients had been assessed for compliance and other causes, which should be done before diagnosing refractory disease.~~ All patients were assessed for compliance and patients with clinically significant concurrent medical conditions were excluded from the trials. The criterion of ≥2 exacerbations in the previous year is not mentioned for SIRIUS, ~~possibly because these patients are receiving mOCS which may reduce exacerbation frequency.~~ as the aim	(1) rewording aligns with the specialist community consensus of loss of control. (2) rewording ensures the CSR and study protocols for 'the trials' is correctly stated: All patients were assessed for compliance and were excluded if they had evidence of 'lack of adherence to controller medications and/or ability to follow physician's recommendations'. This was in addition to having to have a well-documented requirement for regular treatment with high dose ICS with or without maintenance OCS, and requirement for additional controller medication besides ICS, e.g., long-acting beta-2 receptor agonist (LABA), leukotriene receptor antagonist (LTRA) or

	of the study was to assess mepolizumab's ability to reduce mOCS dose, and thus the associated side effect burden, independent of exacerbation baseline frequency, which may be reduced in patients on mOCS.	theophylline. Please see DREAM and MENSA CSR for full inclusion and exclusion details. In addition patients with other clinically significant concurrent medical conditions were excluded from the trials. Please see DREAM and MENSA CSR for full inclusion and exclusion details. 3rd rewording ensures the CSR and study protocols for 'SIRIUS' is correctly reflected.

Issue 21 Lung function selection criteria

Description of problem	Description of proposed amendment	Justification for amendment
3.1.2 GlaxoSmithKline (GSK) clinical trial evidence (ITT population), page 24: Misinterpretation of Forced expiratory volume in 1 second (FEV1) <80% as a selection criterion for all three mepolizumab trials.	Forced expiratory volume in 1 second (FEV1) <80% was a selection criterion for all three mepolizumab trials. Severe refractory eosinophilic patient eligible for mepolizumab are at the severe of the disease spectrum and thus many have fixed airway obstruction. However, the clinical advisors to the ERG noted that patients can have multiple exacerbations whilst having an FEV1 of 80% or greater. ~~As such~~,While patients with FEV1>80% are missing from the clinical evidence submitted by the company, the vast majority of patients eligible for mepolizumab will be covered in the trial evidence.	Patients eligible for mepolizumab are severe asthmatic at step 4 and 5 of the BTS/SIGN treatment algorithm. These patients are of greatest need and most are expected to have fixed airflow limitations as supported by clinical specialists when designing the clinical trials.

Issue 22 Previous exacerbations in the GSK PP and the subgroup analyses

Description of problem	Description of proposed amendment	Justification for amendment
3.1.3 GSK Proposed Populations, page 26 and 4.2.3.2 Subgroup analyses, Previous exacerbations threshold, Page 71: Factually inaccurate definition of exacerbations in the GSK PP and subgroup analysis	3.1.3 GSK Proposed Populations, page 26 reword: ~~Previous exacerbations (in the GSK PP and the subgroup analyses) are defined in the clarification response (additional clinical question b) as exacerbations requiring systemic corticosteroids (or for subjects on mOCS, a two-fold or greater dose increase). It should be noted that this is different to the definition of clinically significant exacerbations as an outcome in the pivotal trials of~~	3.1.3 GSK Proposed Populations, page 26: The wording is suggested to ensure the definition of previous exacerbations in the GSK PP and the subgroup analyses is correctly reflected. This definition is the same that was used as an outcome in the pivotal trials so the ERG statement is incorrect..

	~~mepolizumab, which includes exacerbations requiring systemic corticosteroids and/or hospitalisations or ED visits.~~ and 4.2.3.2 Subgroup analyses, Previous exacerbations threshold, Page 71 reword: ~~Previous exacerbations are defined as exacerbations requiring systemic corticosteroids (or for subjects on mOCS, a two-fold or greater dose increase). It should be noted that this is different to the definition of clinically significant exacerbations used in the trials, which includes exacerbations requiring systemic corticosteroids and/or hospitalisations or ED visits.~~ To: Previous exacerbations (in the GSK PP and the subgroup analyses) are defined as exacerbations requiring systemic corticosteroids (or for subjects on mOCS, a two-fold or greater dose increase) and/or hospitalisations or ED visits.	

Issue 23 Statistical analysis SIRIUS

Description of problem	Description of proposed amendment	Justification for amendment
4.2.2.3 Statistical analysis in included studies, page 41: Factually incorrect statement.	4.2.2.3 Statistical analysis in included studies, page 41 – reword: The CS provides details of controlling for multiplicity across treatment comparisons and primary and secondary endpoints in DREAM and MENSA, presumably for the ITT analyses (CS p53-56). ~~However, this is not mentioned in the CS for SIRIUS~~. In SIRIUS no pre-specified multiplicity adjustment was performed.	To ensure correct representation of SIRIUS CSR and protocol.

Issue 24 ED exacerbations

Description of problem	Description of proposed amendment	Justification for amendment
4.2.3.1 Clinical effectiveness in ITT and GSK populations, Clinically significant exacerbations, page 50: Factually incorrect statement	Recommend deletion of this paragraph as incorrect ~~Clinical advisors to the ERG advised that exacerbations requiring either systemic corticosteroids or hospitalisation were more robust indicators of a severe exacerbation than ED visits, because some patients~~	ED visits had to be confirmed to be an asthma exacerbation. ED attendances for other reasons were not counted as an exacerbation. As stated in the trial CSRs, an objective assessment of each recorded event ensure the

	~~may visit the ED for minor reasons such as loss of an inhaler. However, clinically significant exacerbations as defined in the CS included ED visits.~~	circumstances were confirmed as asthma exacerbations. Please see trail CSR for details.

Issue 25 PK/PD study (MEA114092)

Description of problem	Description of proposed amendment	Justification for amendment
4.2.4.1 Description of open-label extension studies, page 76: Factually incorrect statement	Suggest rewording: PK/PD study (MEA11409240) evaluating the PK/PD relationship for different doses and formulations of mepolizumab (75mg IV; 12.5mg, 125mg and 250mg SC) in severe asthma patients on high dose ICS with blood eosinophils >300/μL or ≥200/μL ~~at screening~~ within 12 months of screening and >300/μL or ≥200/μL at screening.	To ensure accuracy in line with CSR page 16, inclusion criteria: 'Subjects with documented evidence of elevated blood eosinophilia levels (>0.3 cells 109/L or ≥0.2 cells 109/L following protocol amendment 1) within 12 months of screening and evidence of elevated blood eosinophilia levels (>0.3 cells 109/L or ≥0.2 cells 109/L following protocol amendment 1) at screening.'

Issue 26 Values in tables

Description of problem	Description of proposed amendment	Justification for amendment
Table 70, Results of the exploratory analyses undertaken by the ERG. 1. Change in costs value for company base case is incorrect: is showing as [redacted], when it should be [redacted]. The ICER however appears to be correct. 2. Change in QALYs in GSK PP excl. stable mOCS, scenario 5, based on your total QALYs should be [redacted], which gives an ICER of £12,431, rather than [redacted] and £17,240 as shown. Also for the same scenario, in GSK PP, based on your totals given, the change in QALYs is [redacted] rather than [redacted], giving an	Please check the calculations in this section and then, if appropriate, revise relevant sections of the report with the correct values.	To ensure the values presented are correct.

ICER of £25,700 rather than £22,239		

Issue 27 Values in table 10

Description of problem	Description of proposed amendment	Justification for amendment
4.2.2.7, Table 10, page 45 Inaccuracy in table 10	**Table 10: Demographic characteristics for ITT populations (CSp66 and Appendix 8.3 and CSRs)**	To ensure the values presented are correct.

	DREAM (N=616)		MENSA (N=576)		
Demographic	**Placebo N=155**	**Mepolizumab All doses N=461**	**Placebo N=191**	**Mepolizumab Both doses N=385**	**I**
Age, yr Mean (SD) Min, max	48.6 (11.28) 15, 74		50.1 (14.28) 12, 82		
Gender, (%) Female	63%		57%		
Race, (%) White	90%		78%		
Body Mass Index, kg/m^2 Mean (SD)	28.5 (5.95)		27.77 (5.830)		
Duration of Asthma, yr Mean (SD)	19.1 (14.3)		19.9 (13.8)		
Blood Eosinophils (cell/µL) Geometric mean	250		290		
Exacerbations in previous year Mean (SD) ≥2 (%) ≥4 (%)	3.6 (3.1) 614 (99.7%) NR		3.6 (2.6) 575 (99.8%) 189 (33%)		4 2
≥1 Exacerbation requiring hospitalisation in previous year (%)	150 (24%)		109 (19%)		
On mOCS (%)	188 (31)		144 (25%)		
Screening Daily OCS Dose Mean (SD), mg	17.4 (16.77)		13.2 (11.89)		

CSR = clinical study report; ED = emergency department; mOCS = maintenance oral corticosteroids; NR = not reported; SC = subcutaneous; SD = standard deviation; yr = years

Issue 28 Values in table 14

Description of	Description of proposed amendment	Justification for

<table>
<tr><th>problem</th><th></th><th>amendment</th></tr>
<tr><td>4.2.3.1, Table 14, page 51
Inaccuracy in table 10 – MENSA exacerbation rate results</td><td>Please change figures in below section of table 14 and text were figures mentioned in ERG report:
<table>
<tr><th></th><th colspan="4">ITT</th></tr>
<tr><th></th><th>Placebo</th><th>Mepo 100mg SC</th><th>Mepo 75mg IV</th><th>Mepo 75 or 100mg</th></tr>
<tr><th></th><th colspan="4">MENSA</th></tr>
<tr><td>N</td><td>191</td><td>194</td><td>191</td><td>385</td></tr>
<tr><td>Rate/year</td><td><s>1.75</s> 1.74</td><td><s>0.81</s> 0.83</td><td>0.93</td><td>0.877 (model)</td></tr>
<tr><td>Rate ratio (mepo/pbo)</td><td></td><td>0.47</td><td>0.53</td><td>0.50</td></tr>
<tr><td>95% CI</td><td></td><td>0.35, <s>0.63</s> 0.64</td><td><s>0.39</s> 0.40, <s>0.71</s>0.72</td><td>0.39, <s>0.64</s> 0.65</td></tr>
<tr><td>p-value</td><td></td><td><0.001</td><td><0.001</td><td><0.001</td></tr>
</table></td><td>To ensure the values presented are correct.</td></tr>
</table>

Issue 29 Values in table 17

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th></tr>
<tr><td>4.2.3.1, Table 17, page 57
Inaccuracy in table 17 – DREAM FEV_1 results</td><td>Please change figures in below section of table 17 and text were figures mentioned in ERG report:

Page 55:
In DREAM, the difference in FEV1 for mepolizumab vs. placebo in the ITT population was <s>much</s> slightly smaller (<s>3</s> 61ml) at 52 weeks than in MENSA (98ml and 100 ml; Table 17); the reason for this is not clear. Data for other DREAM populations, or for other sub-populations and meta-analyses, were not reported in the CS or requested by the ERG (Table 17).

Page 57:
<table>
<tr><th></th><th colspan="4">ITT</th></tr>
<tr><th></th><th>Placebo</th><th>Mepo 100mg SC</th><th>Mepo 75mg IV</th><th>Mepo 75 or 100mg</th></tr>
<tr><th></th><th colspan="4">MENSA</th></tr>
<tr><td>N</td><td>189</td><td>192</td><td>188</td><td>380</td></tr>
<tr><td>LS mean (SE)</td><td>1907 (31.4)</td><td>2005 (31.1)</td><td>2007 (31.5)</td><td>2006 (22.1)</td></tr>
<tr><td>LS mean change (SE)</td><td>86 (31.4)</td><td>183 (31.1)</td><td>186 (31.5)</td><td>184 (22.1)</td></tr>
<tr><td>Difference (mepo-pbo)</td><td></td><td>98</td><td>100</td><td>99</td></tr>
<tr><td>95% CI</td><td></td><td>(11, 184)</td><td>(13, 187)</td><td>(23, 174)</td></tr>
<tr><td>p-value</td><td></td><td>0.028</td><td>0.025</td><td>0.010</td></tr>
<tr><th></th><th colspan="4">DREAM</th></tr>
<tr><td>N</td><td><s>154</s> 127</td><td></td><td><s>152</s> 129</td><td><s>152</s> 129</td></tr>
<tr><td>LS mean (SE)</td><td><s>2021</s> 1942 (37.7)<s>(37.6)</s></td><td></td><td><s>2024 (37.6)</s> 2003 (37.6)</td><td><s>2024 (37.6)</s> 2003 (37.6)</td></tr>
</table></td><td>To ensure the values presented are correct.</td></tr>
</table>

	LS mean change (SE)	~~139~~ 60 (37.7)~~(37.6)~~		~~142 (37.6)~~ 121 (37.6)	~~142 (37.6)~~ 121 (37.6)		
	Difference (mepo-pbo)			**~~3~~ 61**	**~~3~~ 61**		
	95% CI			~~(-97, 102)~~ (-39, 161)	~~(-97, 102)~~ (-39, 161)		
	p-value			~~0.958~~ 0.229	~~0.958~~ 0.229		

Issue 30 Values in table 31

Description of problem	Description of proposed amendment	Justification for amendment
4.2.3.1, Table 31, page 78 Inaccuracy in table 31	Please change figures in below section of table 31 and text were figures mentioned in ERG report: Page 77: A total of 998 patients have been enrolled in COSMOS (N=651) and COLUMBA (N=347; Table 31). More than half of the patients who participated in DREAM (347/616, 56%) enrolled in COLUMBA, with a ≥12 month treatment break between the two studies. Most patients from MENSA (~~522~~ 525/576, 91%) and SIRIUS (126/135, 93%) elected to continue treatment and directly rolled over into COSMOS. Page 78: **Table 31: Patient numbers in open-label extension studies COSMOS and COLUMBA (CS p153-4)**	To ensure the values presented are correct.

	Receiving mepolizumab 100mg SC	
Trial	**COLUMBA (interim)**	**COSMOS (final)**
% enrolling from RCTs	From DREAM: 347/616 (56%)	From MENSA: ~~522~~ 525/576 (91%) From SIRIUS: 126/135 (93%)
Previous treatment		Previous mepolizumab: 414 Previous placebo: 237
N enrolled	**347**	**651**
Withdrawn	22 (6%)	66 (10%)
Continuing treatment (interim)	325 (94%)	N/A
Completed	N/A	585 (90%)

	Primary reason for withdrawal, N (%): Adverse event Withdrew consent Lack of efficacy Protocol deviation Physician decision Lost to follow-up Met protocol stopping criteria	 ~~11(2)~~ 8(2) ~~14 (2)~~ 8 (2) ~~19 (3)~~ 0 ~~8 (1)~~ 2 (<1) ~~9 (1)~~ 1 (<1) ~~3 (<1)~~ 2 (<1) ~~2 (<1)~~ 1 (<1)	 11 (2) ~~8 (2)~~ 14 (2) ~~8 (2)~~ 19 (3) ~~0~~ 8(1) ~~2 (<1)~~ 9 (1) ~~1 (<1)~~ 3 (<1) ~~2 (<1)~~ 2 (<1) ~~1 (<1)~~	

1 SC = subcutaneous

Issue 31 Cut off dates for OLEs

Description of problem	Description of proposed amendment	Justification for amendment
Section 4.2.5, page 82 Incorrect date for COSMOS and COLUMBA data cut off	Please change text where mentioned in ERG report: *4.2.5 Safety of mepolizumab* The CS provided a review of safety evidence and AEs for mepolizumab. Results were presented for the placebo-controlled trials (DREAM, MENSA and SIRIUS) and the non-randomised, non-controlled, open-label extension studies (COSMOS and COLUMBA). Data collection has been completed for COSMOS but is ongoing for COLUMBA (data cut-off of ~~23rd September 2015~~ 28th February 2014).	To ensure the date presented is correct.

Issue 32 Effect of antibodies

Description of problem	Description of proposed amendment	Justification for amendment
Section 4.2.5.7, page 88 Incorrect statement	Please change as below: In both the placebo-controlled trials and open-label studies, 5%-6% of patients treated with mepolizumab 100mg SC developed anti-mepolizumab antibodies. ~~although the implications of this are unclear.~~ Antibodies did not discernibly impact upon the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level.	To ensure the date presented is correct. As stated in the ERG report on page 87: 'It was reported that the anti-mepolizumab antibodies did not discernibly impact upon the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level.

Issue 33. Confidentiality

Description of problem	Description of proposed amendment	Justification for amendment
P151 shows what the extra QALY gain would need to be to meet the ICER threshold of £30k/£20k. This potentially enables back calculation of cost.	Please can you mark as confidential the [redacted] and [redacted] values.	Removes the potential for back calculation.