Mepolizumab for treating severe eosinophilic asthma: A Single Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
	Iñigo Bermejo, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
	Katy Cooper, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
	Sue Harnan, Research Fellow, ScHARR, University of Sheffield, Sheffield, UK
	Jean Sanderson, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
	Mark Clowes, Information Specialist, ScHARR, University of Sheffield, Sheffield, UK
	Christopher Carroll, Reader in Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
	Tim Harrison, Clinical Associate Professor and Honorary Consultant, Nottingham Respiratory Research Unit, University of Nottingham, Nottingham, UK
	Shironjit Saha, Consultant Respiratory Physician, Sheffield Teaching Hospitals NHS Foundation Trust, Northern General Hospital, Sheffield S5 7AU, UK
Correspondence Author	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
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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.

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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

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	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 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

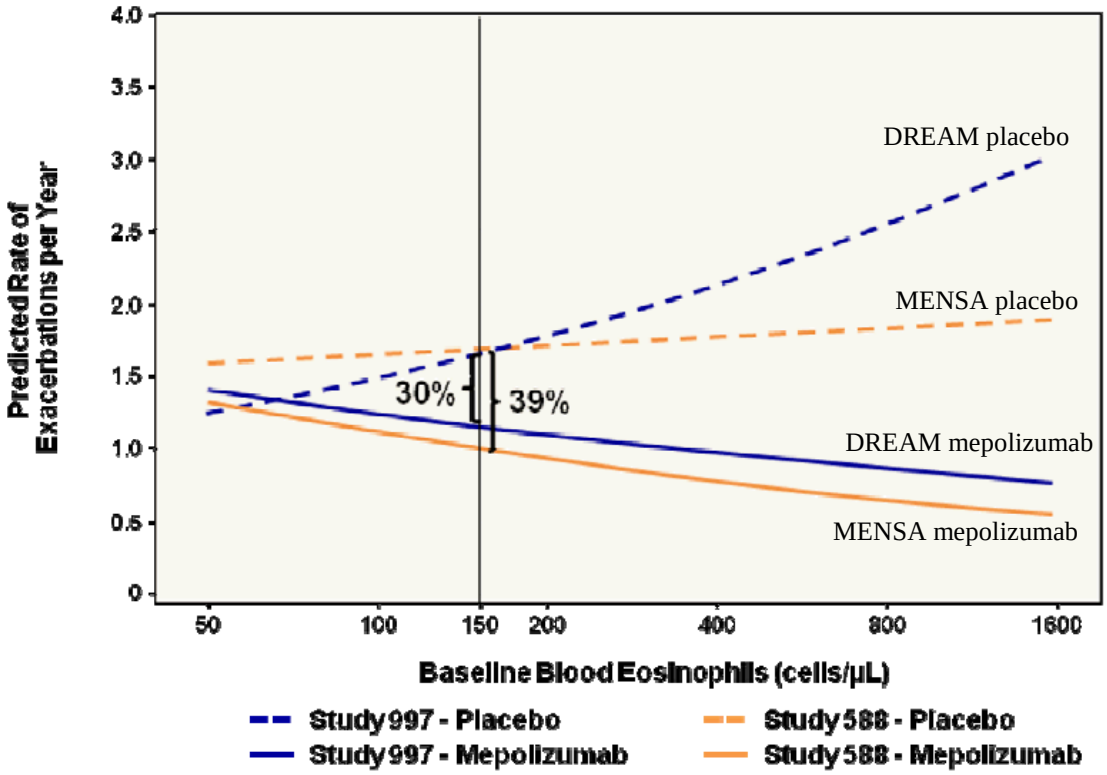
Multivariate modelling of DREAM data showed that the covariates influencing the number of exacerbations (as selected using backwards selection at the 5% significance level) were: treatment, number of exacerbations in the year prior to baseline, randomisation stratum (stable OCS use at baseline or not), 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.

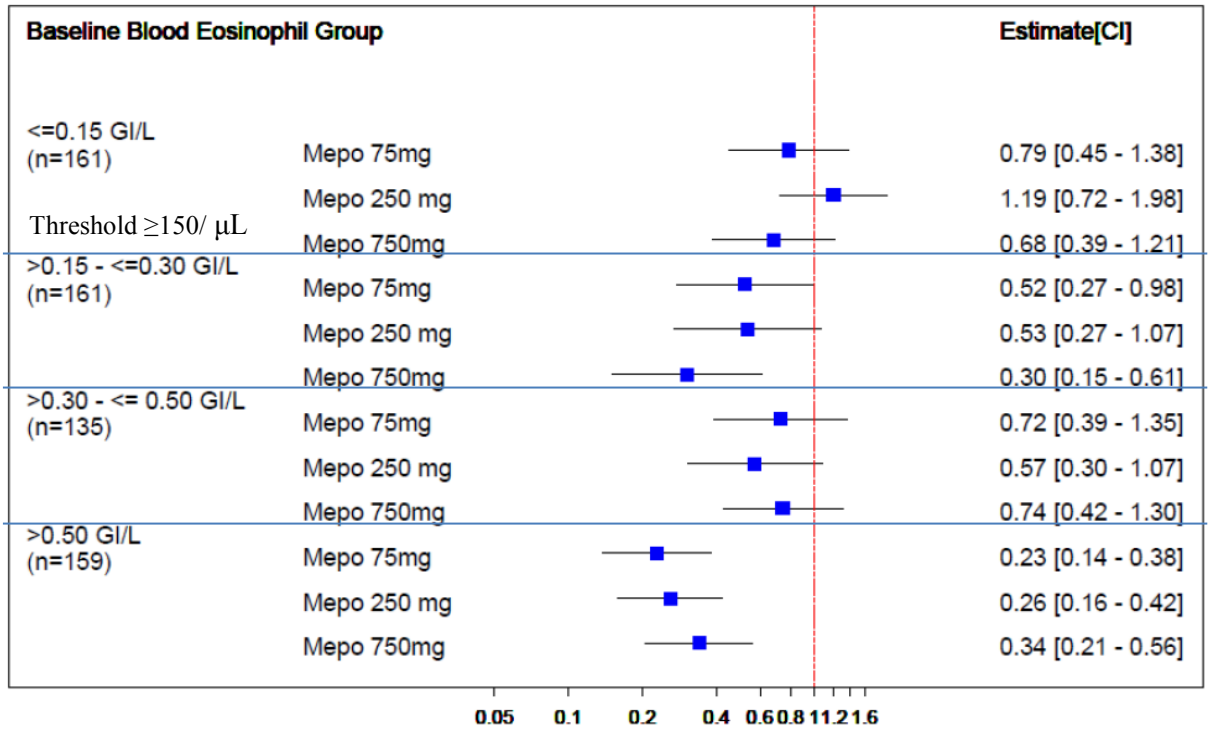
Table 25: Analysis of rate of clinically significant exacerbations by blood eosinophil criteria (MENSA, adapted from CS p103 Table 44)

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

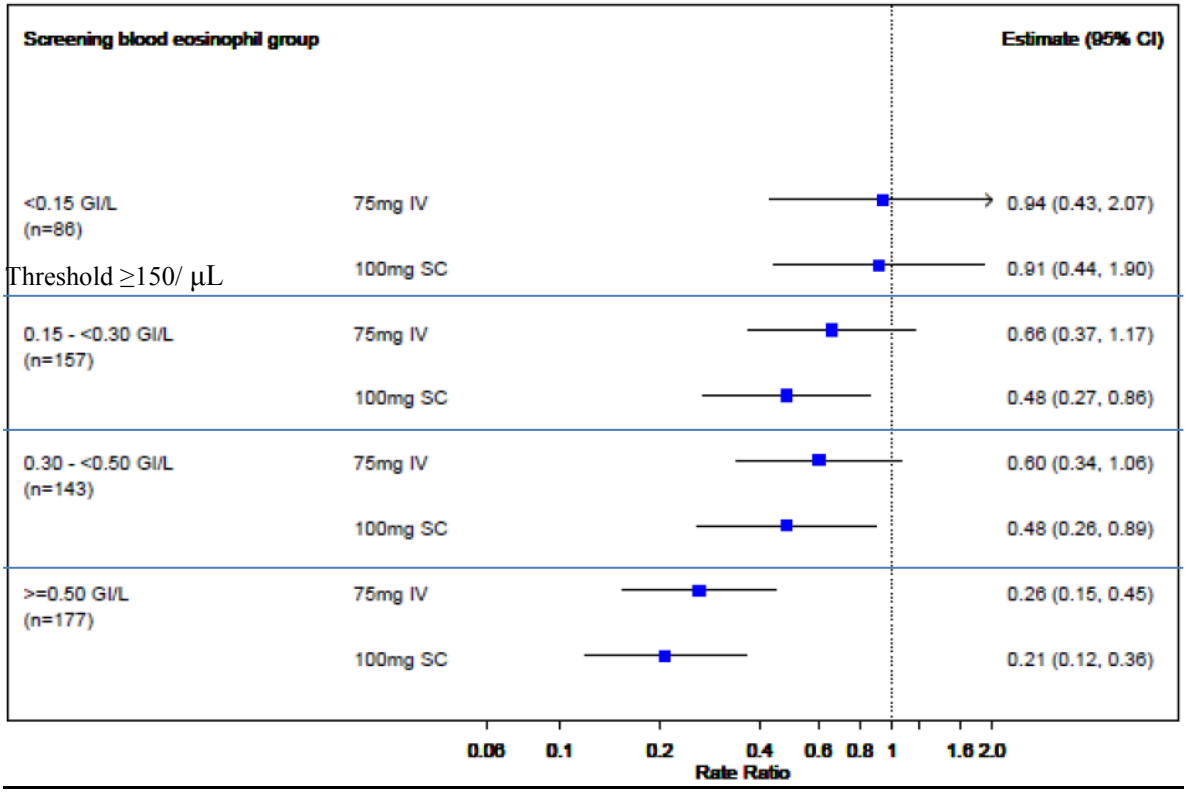
Figure 2 (DREAM, CS p105) and Figure 3 (MENSA, CS p106) illustrate the RRs for exacerbations (mepolizumab vs. placebo) for patients grouped by blood eosinophil count. For each figure, the top horizontal line indicates the ≥150/µL threshold. It can be seen that in both studies, the RR for exacerbations 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)

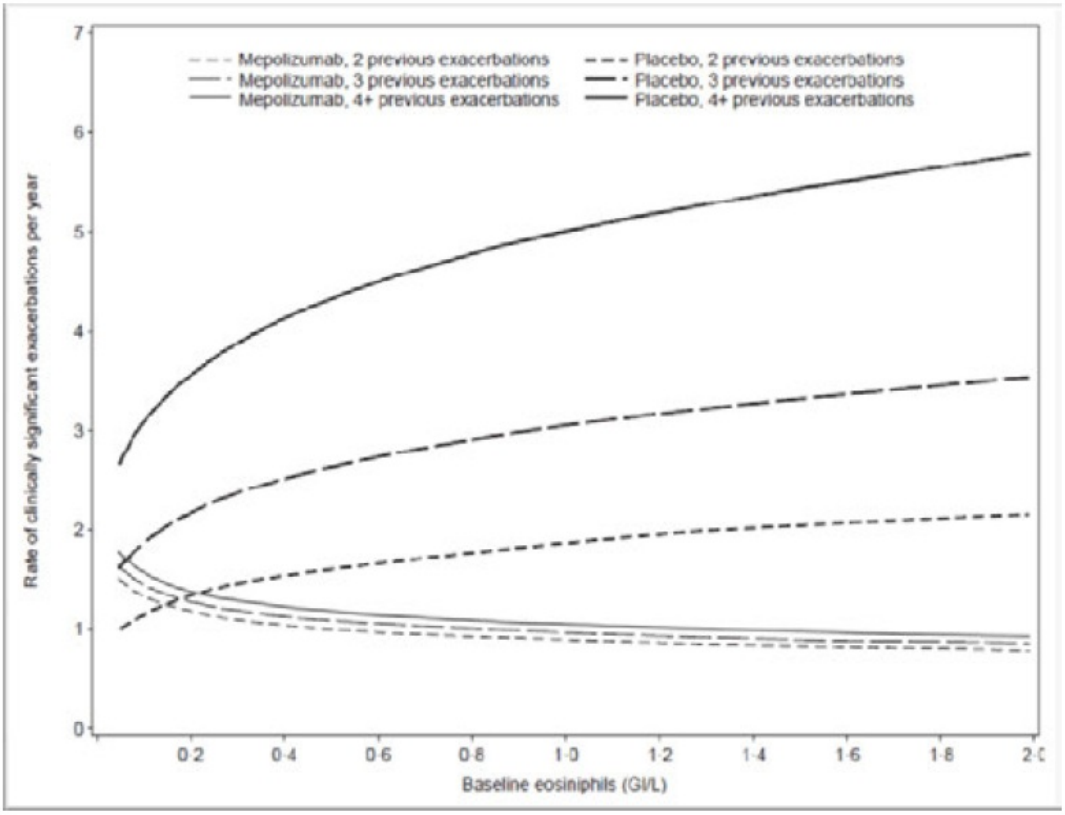
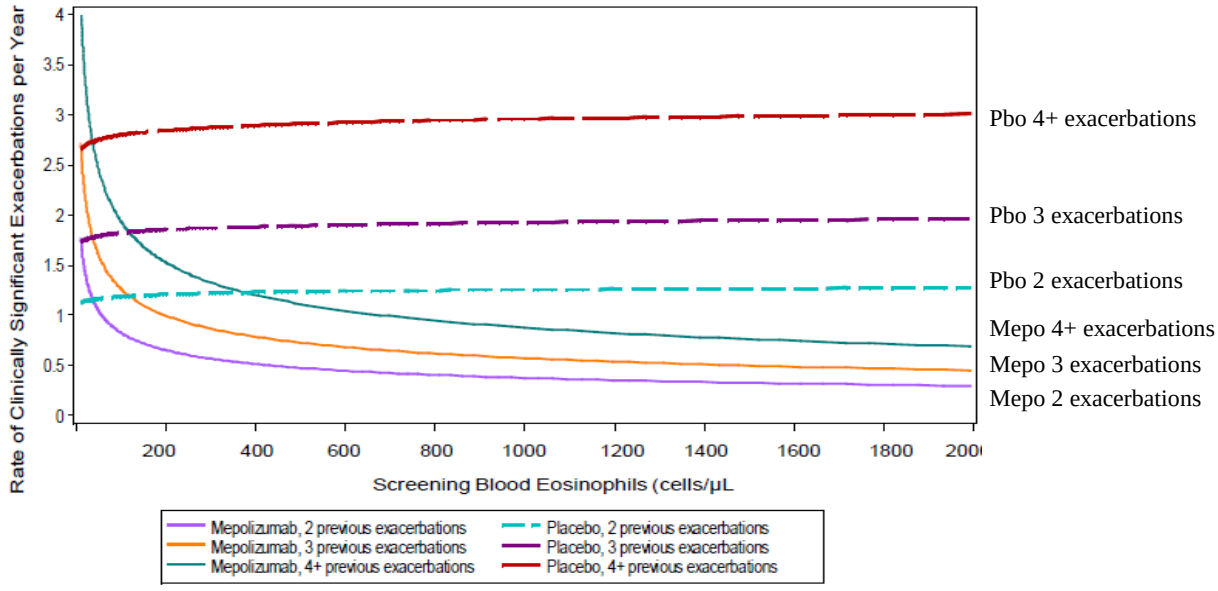


Figure 5: Predictive modelling of exacerbation rate based on screening blood eosinophil count, history of exacerbations and treatment with mepolizumab or placebo (MENSA, CS Figure 8)



CS states: Figure adapted from Ortega *et al*. 2014. Mepo = mepolizumab; Pbo = placebo

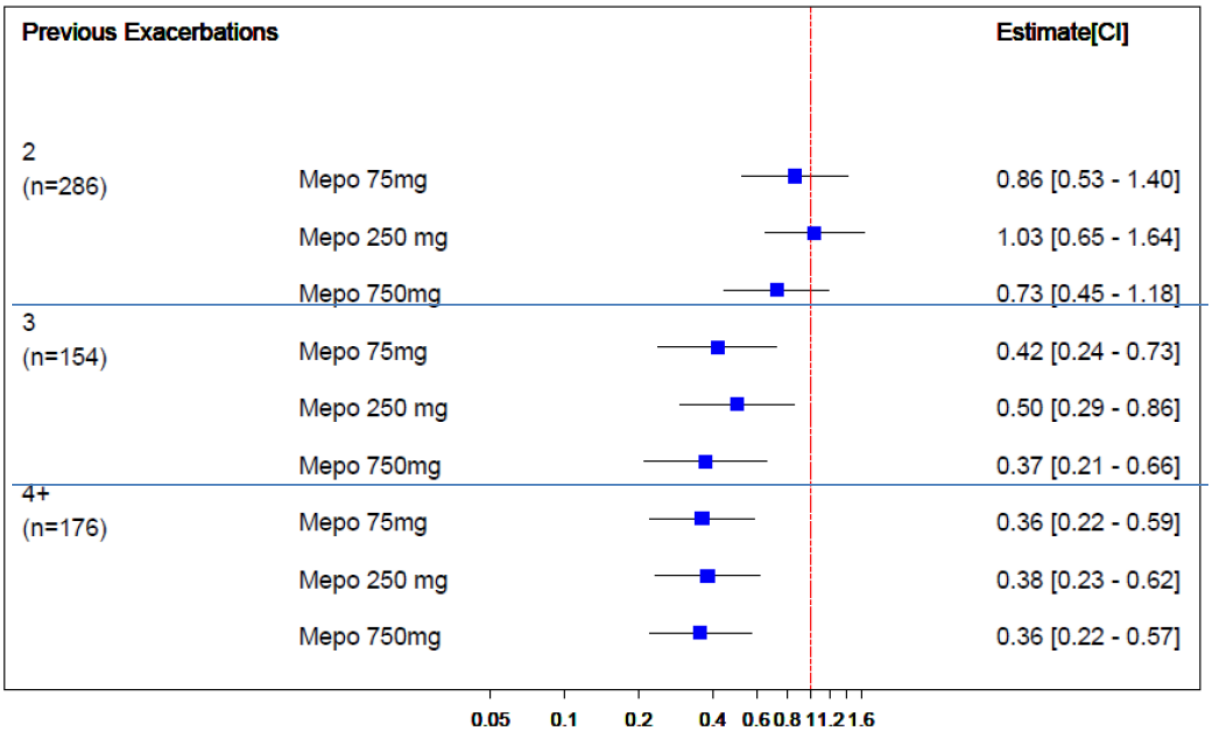
Previous exacerbations threshold

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)

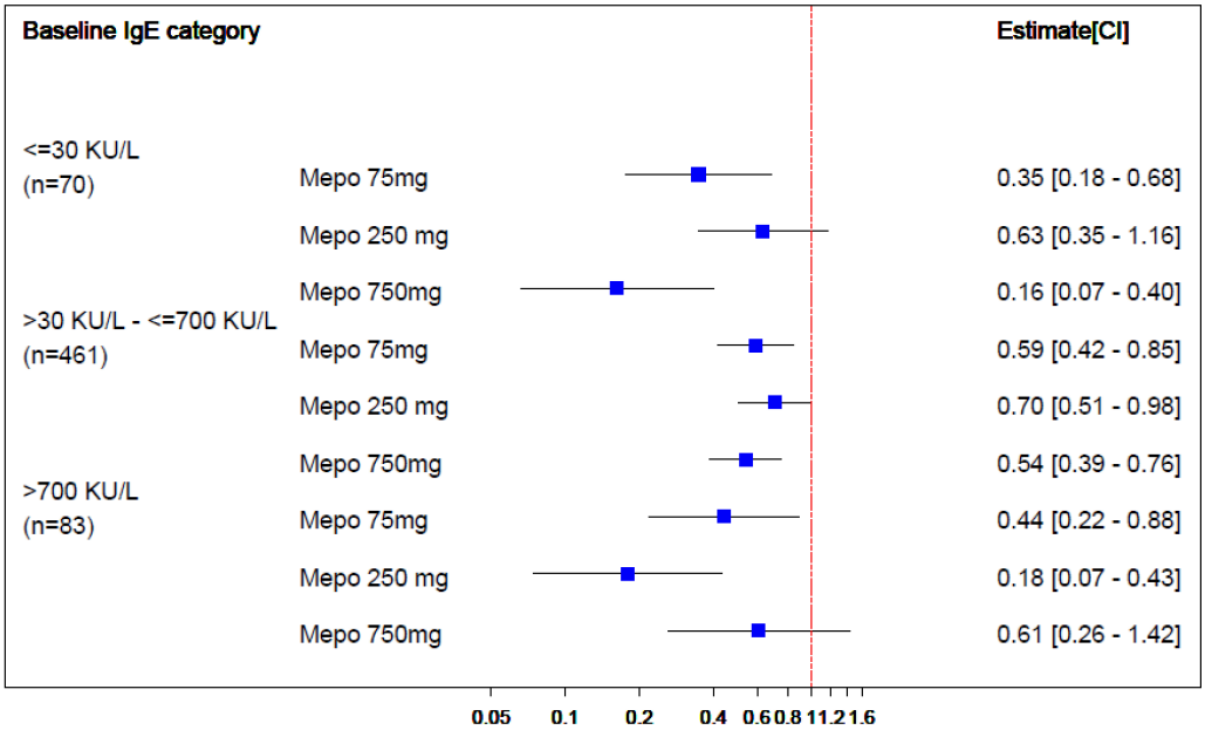
Baseline mOCS therapy	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
No			
N Exacerbation rate/year	147 1.60	143 0.85	142 0.55
Comparison vs. placebo			
RR (mepolizumab/placebo) 95% CI		0.53 0.37, 0.76	0.34 0.23, 0.51
Yes			
N Exacerbation rate/year	44 2.16	48 1.12	52 1.73
Comparison 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 $\leq$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

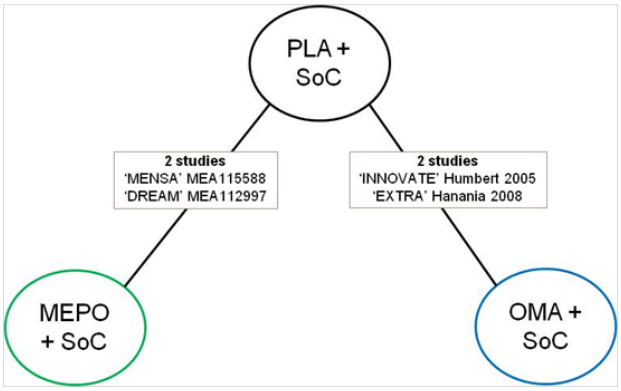
4.4 Critique of the indirect comparison and/or multiple treatment comparison

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.

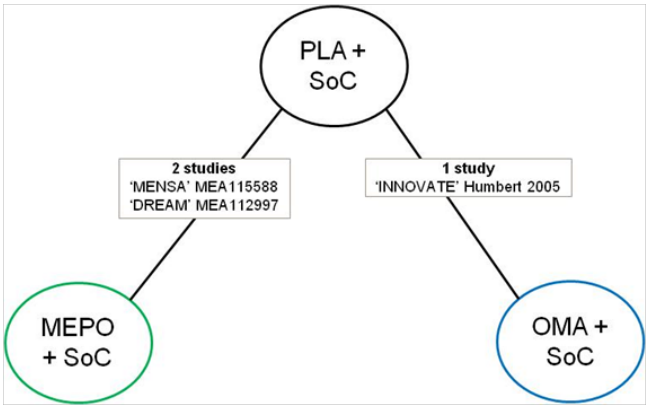
Network diagrams for these analyses based on the `full trial' Population 3, and Scenario 1 (double-blind RCTs, mepo 100mg SC + 75mg IV) are shown in Figure 8 (clinically significant exacerbations) and Figure 9 (exacerbations requiring hospitalisation and change from baseline in predicted FEV_1). The 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.

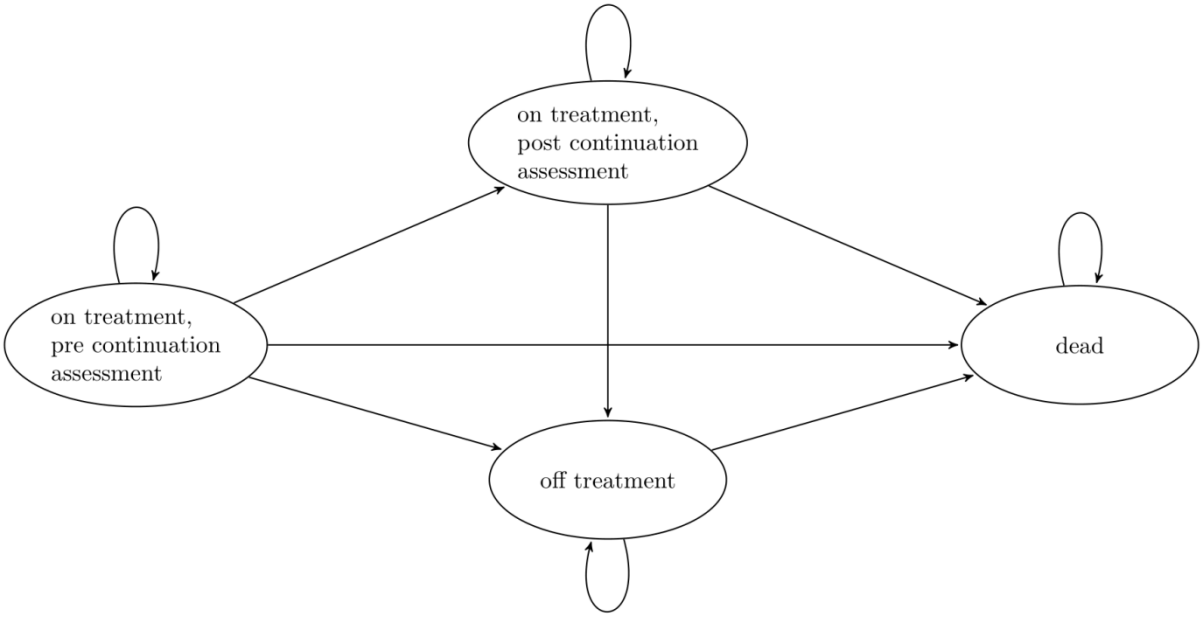
5.2.5 Model structure

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 51 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 50. 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 52). 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 53) 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 54. 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.

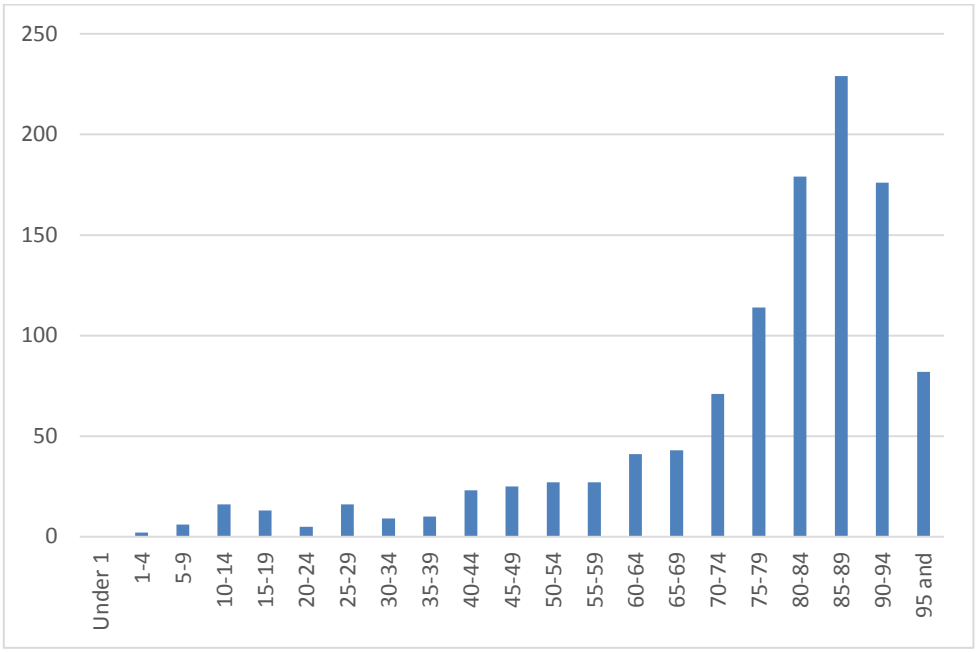
The ERG notes that the age stratification in Watson *et al*.[1] fails to capture the increase of asthma-related mortality rates observed after the age of 45. In Roberts *et al*.[2] patients above the age of 45 are stratified into three ranges (45–54 years; 55–64 years; and 65 years and over) and the 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 55 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 56 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 57 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 58 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 59. 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 60. 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 61 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 62). 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)

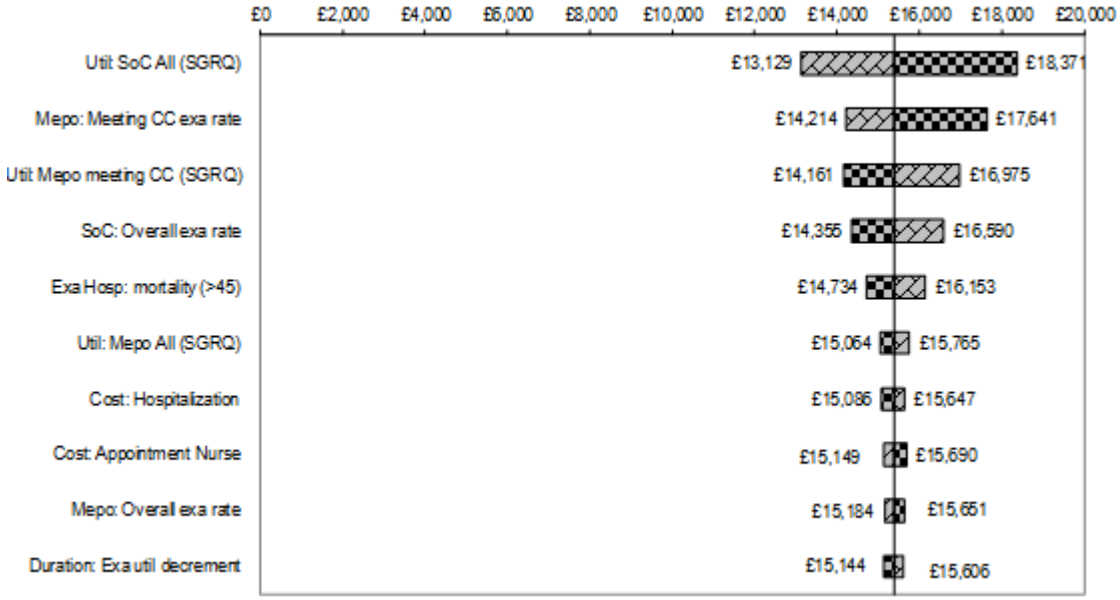


Figure 13: ICER for mepolizumab versus SoC alone; GSK proposed population (reproduced from CS Figure 34)

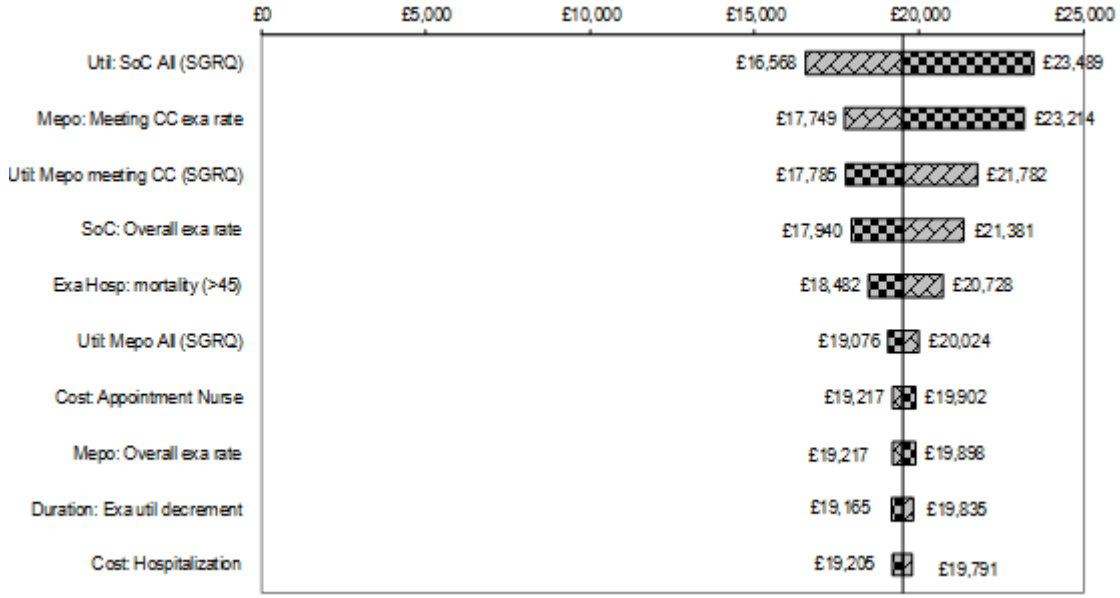


Figure 14: ICER mepolizumab versus omalizumab; Full ITT (reproduced from CS Figure 35)

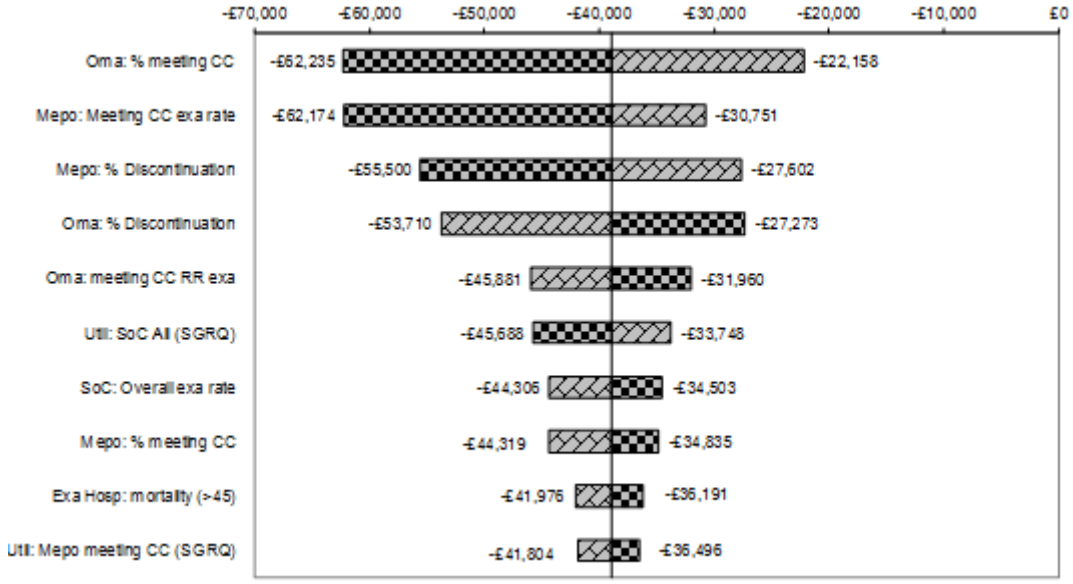
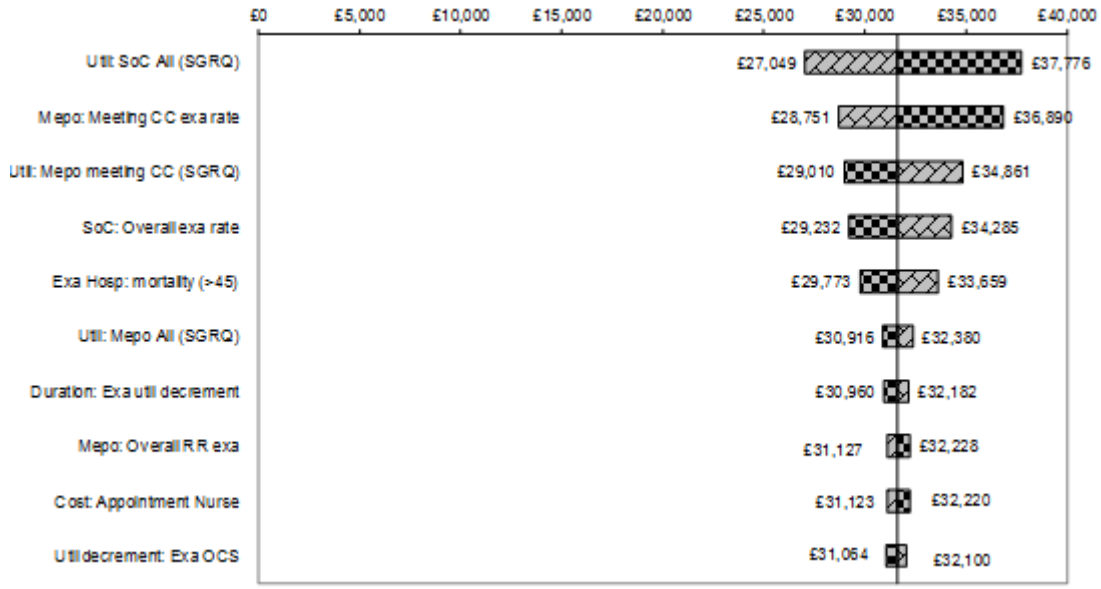


Figure 15: ICER mepolizumab versus SoC alone; Full ITT (reproduced from CS Figure 36)



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 63.

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]				15,690	[redacted]				19,963
Discontinuation beyond year 1: 0%										
Mepo	[redacted]					[redacted]				
SoC	[redacted]				15,305	[redacted]				19,326
Discontinuation beyond year 1: 20%										
Mepo	[redacted]					[redacted]				
SoC	[redacted]				15,516	[redacted]				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 64, 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 65). 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 66.

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 68. 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]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	15,394	[redacted]	[redacted]	[redacted]	[redacted]	19,526
Asthma related mortality: Watson *et al.* / Roberts *et al.* (option 1)										
Mepo	[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	20,203	[redacted]	[redacted]	[redacted]	[redacted]	26,648
Asthma related mortality: Watson *et al.* / Roberts *et al.* (option 2)										
Mepo	[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	20,735	[redacted]	[redacted]	[redacted]	[redacted]	27,544
DREAM population (EQ-5D utilities)										
Mepo	[redacted]		[redacted]			[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	16,907	[redacted]	[redacted]	[redacted]	[redacted]	17,630

Meta-analysis of MENSA and DREAM (EQ-5D utilities)										
Mepo	[redacted]									
SoC	[redacted]				17,269					19,932
Meta-analysis of MENSA and DREAM (SGRQ-mapped utilities)										
Mepo	[redacted]									
SoC	[redacted]				14,679					18,779
Using the SGRQ-mapped utilities from SIRIUS (exacerbation rates from MENSA)										
Mepo	N/A		N/A							
SoC	N/A	N/A	N/A	N/A	N/A					32,374
No disutilities from exacerbations										
Mepo	[redacted]									
SoC	[redacted]				16,010					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 65).

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 69.

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 67). 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 70 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 70. The ERG's base case combines the four scenario analyses with the use of rates from COSMOS. Table 70 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)

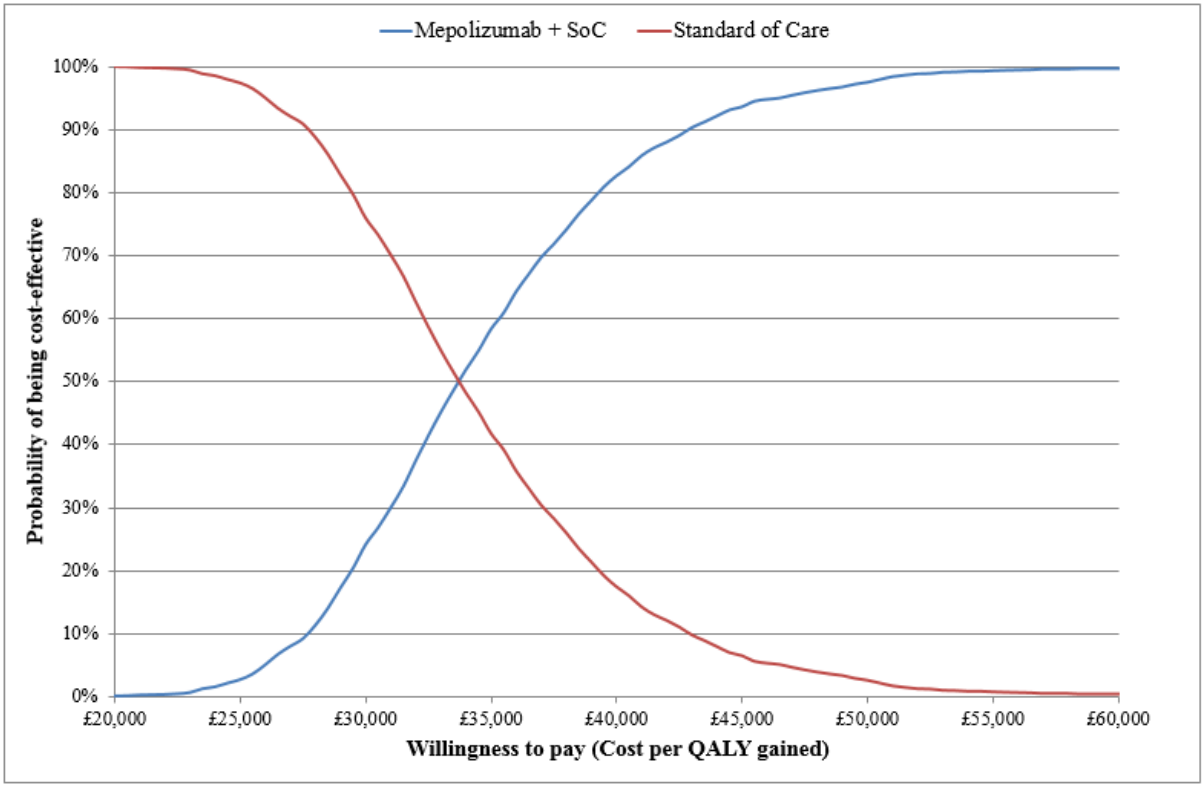
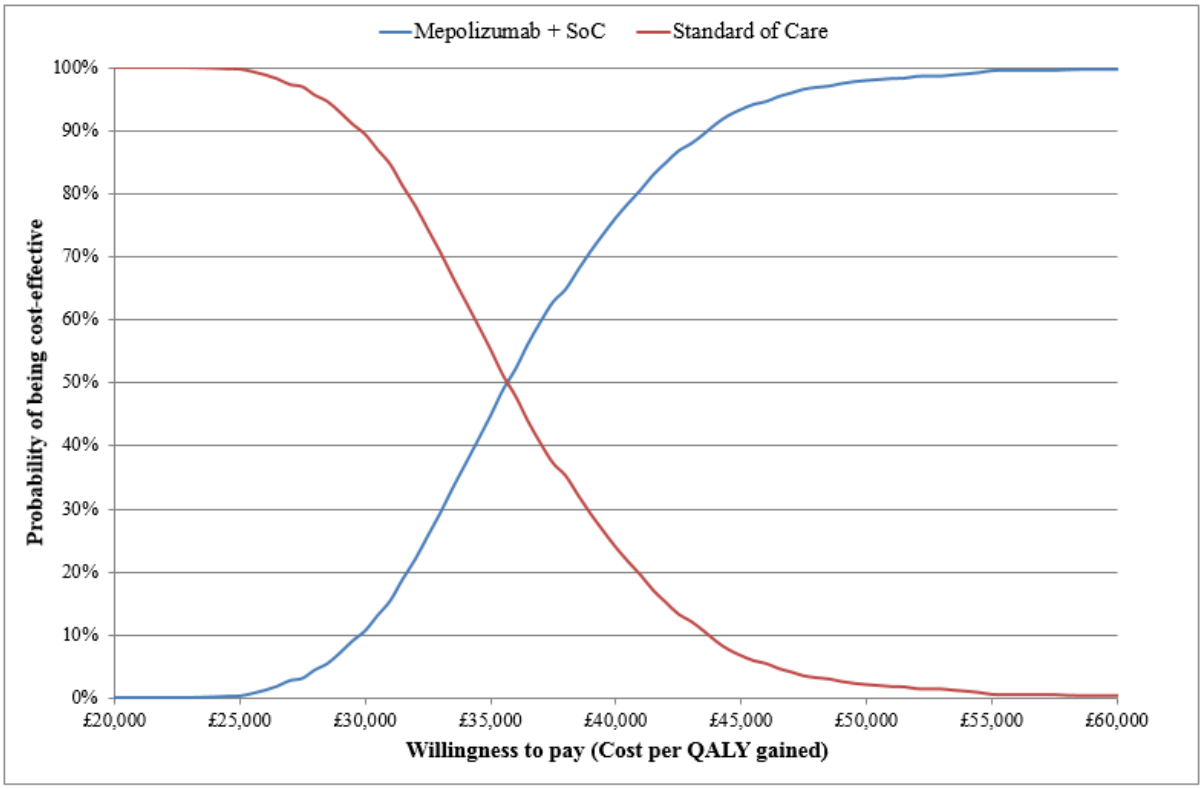


Figure 17: Cost-effectiveness acceptability curve for the GSK PP (ERG's base case)



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 71 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 71 contains those produced by the company's base case, whilst the final row of results represents the ERG base case. From Table 71, 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 70. 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 72).

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 70. 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 67). These exploratory resulted in the ICERs shown in Table 73. 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]			[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]			[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 74). 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 70					
	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 70					
	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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