Mepolizumab for treating severe eosinophilic asthma: A Single Technology Appraisal

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For exacerbations requiring hospitalisation, RRs for mepolizumab (100mg SC and 75mg IV groups combined) vs. placebo, meta-analysed across MENSA and DREAM, were: RR=0.50 (95% CI 0.28, 0.89) in the ITT population; RR=0.44 (95% CI 0.19, 1.02) in the GSK PP; RR=0.43 (95% CI 0.16, 1.12) in the GSK PP excl. stable mOCS; and RR=0.53 (95% CI 0.10, 2.75) in the stable mOCS population. In SIRIUS, hospitalisation numbers were low (ITT: 7 for placebo vs. 0 for mepolizumab). Exacerbations requiring hospitalisation or ED visits showed a similar pattern. In terms of quality of life, differences on the St. George's Respiratory Questionnaire (SGRQ) for MENSA and SIRIUS for mepolizumab vs. placebo ranged from 5.0 to 12.8 units ($p<0.001$ for meta-analysed results), in all sub-populations except in stable mOCS patients where the difference ranged from 1.2 to 5.8 ($p=0.106$). The minimal clinically important difference [MCID] is 4 units. Differences on the Asthma Control Questionnaire (ACQ) meta-analysed across trials ranged from -0.34 to -0.78 ($p<0.001$ for all) across all sub-populations except in stable mOCS patients where the difference was ranged from 0.30 ($p=0.144$) to 0.43 ($p=0.007$) (MCID 0.5 units).

Steroid reduction: The SIRIUS trial had a primary endpoint of percentage reduction in OCS dose whilst maintaining asthma control. Odds ratios (OR) for mepolizumab vs. placebo were: OR=2.39 (95% CI 1.25, 4.56) for ITT; OR=1.81 (95% CI 0.86, 3.79) for GSK PP; OR=2.75 (95% CI 0.72, 10.59) for GSK PP excl. stable mOCS. Absolute differences between mepolizumab and placebo for the proportion achieving a reduction in OCS dose whilst maintaining asthma control were 20% in the ITT population, 13% in the GSK PP, and 26% in the GSK PP excl. stable mOCS.

In terms of secondary outcomes in the GSK PP, the OCS dose was reduced by at least 50% in 48% of patients (mepolizumab) vs. 38% (placebo), giving an OR of 1.60 (95% CI 0.70, 3.64) and an absolute difference of 10%. A reduction in OCS dose to ≤5 mg was observed in 50% of patients (mepolizumab) vs. 40% (placebo), with an OR of 1.64 (95% CI 0.68, 3.93) and an absolute difference of 10%. In addition, OCS use was stopped completely in 13% (mepolizumab) vs. 8% (placebo), with an OR of 1.35 (95% CI 0.32, 5.78) and an absolute difference of 5%. Results were not significant in the GSK PP ($p>0.1$), though numbers were small. ORs and absolute differences were slightly more favourable in the ITT population than the GSK PP, and were generally statistically significant in the ITT population. Results in the GSK PP excl. stable mOCS were slightly more favourable than in the GSK PP but did not reach statistical significance, though numbers were small.

Subgroup analyses: *Post hoc* subgroup analyses and modelling were used to identify the two GSK proposed populations. The CS compares two options for eosinophil threshold: ≥150/μL at screening or ≥300/μL in the previous 12 months. Patients with ≥150/μL at screening had a greater reduction in exacerbations for mepolizumab vs. placebo than patients with <150/μL; this was not the case when the population was subgrouped using a threshold of ≥300/μL in the previous 12 months. The company

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Clinical validity of sub-populations: The CS states that the thresholds for eosinophil level and previous exacerbations were clinically plausible and practical to implement according to severe asthma specialists. In terms of eosinophil level, the European Medicines Agency (EMA) concluded that eosinophil levels were not sufficiently predictive to justify a specific cut-off within their marketing authorisation. Clinical advisors to the ERG advised that a threshold of ≥300 cells/μL in the previous 12 months would be more appropriate for the diagnosis of eosinophilic asthma than ≥150/μL at screening, firstly because 150/μL is within the normal range and secondly because eosinophil levels can fluctuate. Clinical advisors to the ERG considered that a threshold of ≥4 previous exacerbations was clinically appropriate, and was consistent with NICE guidance for omalizumab which restricts the use of the drug to people requiring continuous or frequent treatment with oral corticosteroids (≥4 courses in the previous year).

Evaluation of the indirect comparison: The indirect comparison methods appear broadly appropriate. However, the ERG considers that the results of the random effects model provide a more appropriate (and more conservative) estimate than those of the fixed effects model given the heterogeneity between trials. The company also acknowledges that the results should be treated with caution since only a small proportion of patients in the mepolizumab and omalizumab trials were eligible for both treatments, and study populations differed in terms of severity.

1.4 Summary of cost effectiveness evidence submitted by the manufacturer

The manufacturer supplied a *de novo* cohort Markov model constructed in Microsoft Excel©. The perspective used was that of the NHS in England. The cycle length was set to four weeks and a lifetime time horizon (approximately 92 years) was used. A discount rate of 3.5% per annum was used both for costs and utilities. The model includes four states: (i) on-treatment before continuation assessment; (ii) on-treatment after continuation assessment; (iii) off-treatment and; (iv) death. All patients on a biologic treatment enter the model in the 'on-treatment before continuation assessment' state, until the continuation assessment. After continuation assessment, patients transition either to 'on-treatment after continuation assessment' or 'off-treatment' depending on whether or not they meet a continuation criteria: patients on mepolizumab continued on treatment unless the exacerbation rate worsened compared with the previous year whilst patients on omalizumab continued only if they achieved a physician-rated global evaluation of treatment effectiveness score of good or excellent. Patients in the 'on-treatment after continuation assessment' state transition to the 'off-treatment' state when they discontinue treatment. All patients on SoC enter the model in the 'off-treatment' state. During any cycle, patients can transition from any of the alive states to death as a consequence of either asthma-related mortality following an exacerbation or due to other causes.

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mepolizumab compared with a group where mOCs had not been added. The SIRIUS trial could have provided an insight for mepolizumab in this comparison, but the analysis using the data from SIRIUS was subject to a high degree of uncertainty due to the small size of the GSK PP in this trial.

The ERG has concerns regarding the continuation criteria defined for mepolizumab. Grammatically this should be a continuation criterion but we have used continuation criteria to be consistent with the CS. According to these, all patients who did not experience a worsening in exacerbation rates would to receive mepolizumab. This implies that a proportion of patients would remain on mepolizumab despite experiencing This implies that a proportion of patients would remain on mepolizumab despite experiencing no numerical improvement in exacerbations, however patients could be receiving benefit in the form of reduced OCS exposure or symptomatic improvement. The ERG also has concerns regarding the calculation of exacerbation rates for patients meeting the continuation criteria: these rates were measured in the MENSA trial shortly after the beginning of treatment, based on a 16-week time span and therefore might not be representative of the long-term effectiveness of mepolizumab and may be affected by seasonality. Furthermore, there may be a regression to the mean.

Regarding the comparison with omalizumab, the ERG notes the importance of the decision taken by the company to use the cost of omalizumab as calculated through a study; this results in an estimated drug cost which was more than 40% higher than that reported within the assessment report of the omalizumab MTA.

For these reasons, the ERG believes that there is considerable uncertainty regarding the true cost-effectiveness of mepolizumab add-on treatment compared to standard of care and omalizumab.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

Clinical trial data were presented for the ITT population and the GSK proposed populations across a range of relevant clinical outcomes. Data were meta-analysed across trials. Whilst there were gaps in the data provided in the CS, more complete data were provided in the clarification response.

The model used appears conceptually appropriate with only a few minor implementation errors. It contained the functionality to assess the impact of changing parameters and relevant structural uncertainties on the ICER. A number of built-in alternative scenarios were included.

1.6.2 Weaknesses and areas of uncertainty

The ERG considers that the *post hoc* analyses used to justify the GSK proposed populations should be interpreted with caution, particularly the eosinophil threshold of ≥150 cells/μL at screening. The results

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of the NMA should also be interpreted with caution, given the heterogeneity between the trials and the fact that only a subset of the trial patients was eligible for both mepolizumab and omalizumab.

The cost-effectiveness results are sensitive to the utility values used in the model and the methods used to model asthma-related mortality. Alternative methods of calculating exacerbation rates for patients meeting the continuation criteria also have a major impact on the ICER.

Both the company and clinicians consulted by the ERG claim a high disutility caused by the side effects of long-term use of OCS, however the scenario analysis undertaken by the company estimates only a very small benefit. The CS states that 'An OCS dose reduction and discontinuation approach were explored but the scenario analyses did not generate the expected upside of sparing patients from OCS.' GSK further states that the results presented in the CS 'are in contrast to those from the approach taken in the NICE omalizumab MTA which showed an improvement [in the ICER] by £4,000-£6,000/QALY gained and £10,000 - £17,000 /QALY gained'. Thus, the true benefits of OCS sparing appear uncertain. However, it is noted that the cessation of OCS use seemed to be greater for omalizumab than for mepolizumab, as described in section 5.2.11.3.

The key uncertainty in the clinical evidence base for mepolizumab versus omalizumab concerns the absence of head-to-head RCTs comparing these drugs. A key uncertainty in the cost-effectiveness modelling is the cost of the omalizumab treatment, which depends on the weight and IgE levels of a patient, and the estimate for the cost of omalizumab used in the company's model is markedly higher than that used in the previous NICE appraisal of omalizumab. In addition, some of the scenario analyses exploring the comparison between omalizumab and mepolizumab resulted in ICERs substantially different to that of the base case.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The probabilistic base case ICERs presented in the CS comparing mepolizumab with SoC were £19,511 and £15,478 per QALY gained for the GSK PP and GSK PP excl. mOCS, respectively. The ERG made five changes to the company's base case. These included: (i) using directly measured EQ-5D scores instead of the scores mapped from SGRQ; (ii) using the asthma-related mortality rates estimated by the company combining the data from Watson *et al.*[1] and Roberts *et al.*[2]; (iii) removing the use of a fixed duration stopping rule for mepolizumab treatment; (iv) calculating the QALY loss due to exacerbations using the average duration of exacerbations observed in MENSA and; (v) setting the exacerbation rates for those meeting the continuation criteria equal to those derived from the COSMOS study. When taken in isolation, each of these changes led to an increase in the ICER, the largest of which was attributable to the modelling of asthma-related mortality. The combined effect of these changes increases the probabilistic ICER from £19,511 per QALY gained to £35,440 per QALY gained ([redacted] QALYs

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gained at a cost of [redacted]) in the GSK PP, and from £15,478 per QALY gained to £33,520 per QALY gained ([redacted] QALYs gained at a cost of [redacted]) in the GSK PP excl. stable mOCS. The ERG notes that using data from the ITT population with ≥4 exacerbations, rather than with an additional criterion of having ≥150 cells/μL at screening, would produce, in the opinion of the ERG, a more plausible ICER for mepolizumab versus SoC. However, the ERG did not have the data required to undertake this analysis.

For the comparison of mepolizumab versus omalizumab, the base case analysis presented in the CS, which does not incorporate the omalizumab PAS, concludes that mepolizumab dominates omalizumab. The ERG applied three alternative assumptions: (i) the cost of omalizumab (without the PAS) was based on that used within the previous NICE appraisal of omalizumab; (ii) the exacerbation RRs were based on a mOCS population, and; (iii) a random effects NMA model was applied. On the basis of this exploratory analysis, the ICER for omalizumab versus mepolizumab was approximately £43,000 per QALY gained. An estimate of the cost-effectiveness of mepolizumab compared to omalizumab when the omalizumab PAS is assumed is provided in a confidential appendix.

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assessment for adherence to therapy before being termed refractory. The criteria relating to compliance was emphasised in the National Institute for Health and Care Excellence (NICE) guidance for omalizumab.[11] The CS assumes that all patients have been diagnosed as severe refractory eosinophilic asthmatic and are optimized on SoC before being considered eligible for add-on mepolizumab therapy.

Severe eosinophilic asthma: Eosinophilic asthma is a distinct phenotype of asthma characterised by tissue and sputum eosinophilia, a thickening of the basement membrane and, often, responsiveness to corticosteroids.[8] It can be present in mild, moderate or severe asthma.[8] It is, however, associated with more severe disease, late onset, atopy and steroid refractoriness. The diagnosis of eosinophilic asthma is problematic in clinical practice. Induced sputum eosinophil levels of 1-3%[8] are commonly interpreted as indicating eosinophilic disease, however, this test is impracticable in routine care. Alternatives include peripheral blood eosinophil counts, fractional exhaled nitric oxide (FeNO), serum immunoglobulin E (IgE), and periostin levels. However, a recent US review[8] reported that these have limited diagnostic accuracy: levels of blood eosinophils >300 cells/μL had a positive predictive value of only 50% in identifying an eosinophilic asthma phenotype (defined as sputum eosinophils of >2%), serum IgE had no correlation with eosinophilia,[12] studies relating to FeNO appeared inconsistent,[13-15] and the diagnostic utility of periostin was promising but is as yet undetermined. Further, a systematic review and meta-analysis of tests for eosinophilia found sensitivities and specificities of 0·66 (95% Confidence Interval (CI) 0·57–0·75) and 0·76 (95% CI 0·65–0·85) for FeNO; 0·71 (95% CI 0·65–0·76) and 0·77 (95% CI 0·70–0·83) for blood eosinophils; and 0·64 (95% CI 0·42–0·81) and 0·71 (95% CI 0·42–0·89) for IgE respectively.[16] One study concluded that thresholds for interpreting blood eosinophils varied greatly.[17] A Dutch study reported blood eosinophil cut-offs from a derivation and validation cohort, and concluded that the best diagnostic accuracy (for identifying sputum eosinophils >3%) was achievable at values of approximately 220 cells/μL for the derivation cohort, though diagnostic accuracy was reduced in the validation cohort.[18]

Despite only moderate diagnostic accuracy being reported for blood eosinophils in the literature, the test is used in clinical practice to monitor disease.[4] There is no national or international consensus on how to interpret such tests; however, clinical advisors to the ERG stated that a level of ≥300 cells/μL in the previous 12 months is a commonly used cut-off. The CS states *"Eosinophilic asthma inflammation can be measured in both blood and sputum, but recent studies have confirmed that late-onset severe refractory eosinophilic asthma can be reliably characterised by establishing blood eosinophil thresholds in the presence of high-dose ICS in a poorly controlled exacerbating phenotype"* (p 25-26), and references two articles[19, 20] to support this statement, both of which are re-analyses of the phase IIb trial, "Dose Ranging Efficacy And safety with Mepolizumab in severe asthma" (DREAM), which forms part of this submission. The ERG concludes that the use of blood

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scope. The CS therefore provides data for the ITT trial populations and also for sub-populations of patients meeting higher thresholds for severity and eosinophil count (Section 3.1.3).

The three pivotal trials are as follows: DREAM (Pavord *et al*., 2012[19]), "Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma" (MENSA, Ortega *et al*., 2014[24]) and "Steroid Reduction with Mepolizumab Study" (SIRIUS, Bel *et al*., 2014[25]). The pivotal trials include patients requiring high-dose ICS plus additional controllers, with or without maintenance oral corticosteroids (mOCS) (DREAM and MENSA) or requiring mOCS (SIRIUS), and as such include severe asthma patients. SIRIUS includes patients on mOCS, which represents a more severe spectrum of patients than DREAM and MENSA. Two of the trials (DREAM and MENSA) also use a criterion of ≥2 asthma exacerbations requiring treatment with systemic corticosteroids in the previous 12 months, which has been accepted as a measure of loss of control by the international consensus statement from the Innovative Medicine Initiative (Bel et al. 2011). All patients were assessed for compliance and patients with clinically significant concurrent medical conditions were excluded from the trials. The criterion of ≥2 exacerbations in the previous year is not mentioned for SIRIUS, as the aim of the study was to assess mepolizumab's ability to reduce mOCS dose, and thus the associated side effect burden, independent of exacerbation baseline frequency, which may be reduced in patients on mOCS.

Forced expiratory volume in 1 second (FEV_1) <80% was a selection criterion for all three mepolizumab trials. However, the clinical advisors to the ERG noted that patients can have multiple exacerbations whilst having an FEV_1 of 80% or greater. As such, patients with FEV_1>80% are missing from the clinical evidence submitted by the company.

Eosinophilic asthmatics are usually defined as those with sputum eosinophils greater than 1-3%,[8] though as this test is difficult to perform in routine practice and is often not used. There is a lack of agreement about what surrogate markers can be used in clinical practice, and at what cut-off patients should be considered to be eosinophilic (see Section 2.1). The licence does not specify an eosinophil cut-off. The trials included in the CS have identified eosinophilic patients using various methods. MENSA and SIRIUS included patients with either blood eosinophils ≥150 cells/μL at screening or eosinophils ≥300 cells/μL in the past 12 months, whilst the earlier DREAM trial included patients with any of four criteria (blood eosinophils ≥300 cells/μL *or* sputum eosinophils ≥3% *or* exhaled nitric oxide (FeNO) ≥50 ppb *or* prompt deterioration of asthma control following ≤25% reduction in inhaled or oral corticosteroid dose in previous 12 months). The company provided data for the ITT population as well as for a more severe population based on eosinophil count and history of exacerbations (see below).

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The company's rationale for the GSK PP is based on a set of *post hoc* modelling analyses and subgroup analyses of DREAM and MENSA, described further in Section 4.2.4.2. Briefly, subgroup analyses of both DREAM and MENSA showed that the reduction in exacerbations for mepolizumab vs. placebo was greater for patients with higher baseline blood eosinophils than for those with lower baseline eosinophils. In addition, the reduction in exacerbations was greater for patients with more previous exacerbations than those with fewer previous exacerbations in DREAM and MENSA. In addition, the company proposes that mOCS users meeting the eosinophil cut-off should be included in this population (even if they had fewer than 4 exacerbations in the past year) since mOCS users are likely to be a severe group and there are documented clinical benefits associated with reducing the use of mOCS.

The company's rationale for also presenting data for the "GSK PP excl. stable mOCS" population is that this population (excluding mOCS users with <4 previous exacerbations) may show greater effectiveness and cost-effectiveness, since the use of corticosteroids may already have reduced exacerbations in mOCS users, therefore there may be less potential to demonstrate a further reduction in exacerbations in these patients. The CS states that the primary objective in mOCS users would be to reduce steroid exposure whilst maintaining asthma control, but that it is challenging to fully capture the benefits of reducing steroid exposure in the clinical and cost-effectiveness analysis.

Clinical validity and feasibility of GSK PP: The CS (p80) states that, based on modelling and subgroup analyses, patients with ≥150 cells/µl baseline blood eosinophils at screening and ≥4 exacerbations in the 12 months prior to screening experienced the most benefit from therapy with add-on mepolizumab, and that *"the clinical viability of this conclusion was supported by independent severe asthma specialists' interpretation of the results."* The CS also states that *"clinical experts agree that this population is plausible and practical to implement in practice"* (CS p12). The statistical validity of the modelling and subgroup analyses is discussed in Section 4.2.4.2.

In terms of previous exacerbations, clinical advisors to the ERG considered that a threshold of ≥4 previous exacerbations was clinically appropriate. The CS also notes (p81) that the GSK PP is consistent with current NICE guidance for omalizumab which restricts use to people requiring continuous or frequent treatment with oral corticosteroids (≥4 courses in the previous year). Previous exacerbations (in the GSK PP and the subgroup analyses) are defined as exacerbations requiring systemic corticosteroids (or for subjects on mOCS, a two-fold or greater dose increase) and/or hospitalisations or ED visits. This is contrary to the definition supplied in the company's clarification response, but is the definition provided in the Fact Check process. Although predictive modelling reported in the CS appears to show a correlation between previous exacerbations and reductions in

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In DREAM and MENSA, for the primary endpoint of exacerbations, for patients who withdrew, all data up to the time of patient withdrawal were included in the analyses. However, there are missing data for the period following withdrawal. The primary analysis made a standard assumption known as the Missing At Random (MAR) assumption. This assumes that future exacerbations for those who withdraw can be predicted from their exacerbation history prior to withdrawal and from the exacerbation rate of similar patients on the same treatment. Two sensitivity analyses were performed in which it was assumed that future exacerbations for patients who withdrew from a mepolizumab arm could be predicted based on the exacerbation rate in the placebo arm, not on the mepolizumab arm. Both analyses showed similar results to the primary analysis. The ERG is satisfied that the potential impact of missing data following withdrawal on the results of the analyses has been considered appropriately.

In SIRIUS, the primary efficacy endpoint was the percentage reduction in OCS dose during weeks 20-24 compared to the baseline dose, whilst maintaining asthma control. This was categorised as follows: 90% to 100% reduction; 75% to <90% reduction; 50% to <75% reduction; >0% to <50% reduction; or no reduction, lack of asthma control, or withdrawal from treatment. This was analysed using a proportional odds model for the above categories of oral steroid reduction, with covariates of region, number of years on oral steroids (<5 years versus ≥5 years), and baseline oral steroid dose. All subjects in the ITT population were included in the ITT analysis, whilst subjects who withdrew early or who had missing data were assigned to the lowest efficacy category. A sensitivity analysis assigning subjects to an efficacy category according to the dose reduction obtained by the time of withdrawal gave a similar result to the primary analysis. Analysis of the proportion of patients with specific reductions in oral steroid dose was performed using a binary logistic regression model with adjustment for covariates. The median percentage reduction in dose was analysed with the use of the Wilcoxon test. In SIRIUS, the rate of clinically significant exacerbations and rate of exacerbations requiring hospitalisation or ED visits were analysed using a negative binomial generalised linear model with a log-link function adjusting for covariates. Exacerbations requiring hospitalisation were not compared between treatment groups as there were no exacerbations requiring hospitalisation in the mepolizumab treatment arm.

The CS provides details of controlling for multiplicity across treatment comparisons and primary and secondary endpoints in DREAM and MENSA, presumably for the ITT analyses (CS p53-56). In SIRIUS no pre-specified multiplicity adjustment was performed.

4.2.2.4 Statistical methods for subgroup analyses

In DREAM and MENSA, exploratory multivariate modelling was performed to investigate baseline variables predictive of the overall number of exacerbations and of differential efficacy of

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Table 1: Demographic characteristics for ITT populations (CS p66 and Appendix 8.3 and CSRs)

	DREAM (N=616)		MENSA (N=576)		SIRIUS (N=135)		
Demographic	**Placebo N=155**	**Mepolizumab All doses N=461**	**Placebo N=191**	**Mepolizumab Both doses N=385**	**Placebo N=66**	**Mepolizumab 100 mg SC N=69**	**Overall N=135**
Age, yr							
Mean (SD)	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							
Mean (SD)	19.1 (14.3)		19.9 (13.8)		20.1 (14.37)	17.4 (11.79)	18.7(13.13)
Blood Eosinophils (cell/µL)							
Geometric mean	250		290		230	250	NR
Exacerbations in previous year							
Mean (SD)	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

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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. Whilst clinically significant exacerbations as defined in the CS included ED visits these had to be confirmed as an asthma exacerbation. ED attendances for other reasons were excluded.

The rate ratios (RRs) for clinically significant exacerbations for mepolizumab (100mg SC and 75mg IV groups combined) vs. placebo, meta-analysed across MENSA and DREAM, were as follows (Table 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.

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Table 2: Results for clinically significant exacerbations

	ITT				GSK PP				GSK PP excl. stable mOCS				Stable mOCS			
	Placebo	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**
	MENSA															
N	191	194	191	385	64	78	65		45	54	48		19	24	17	
Rate/year	1.74	0.83	0.93	0.877 (model)	2.65	1.32	1.06	1.206 (model)	3.10	1.22	1.20	1.213 (model)	1.4	1.3	0.63	
Rate ratio (mepo/pbo)		**0.47**	**0.53**	**0.50**		**0.50**	**0.40**	Not provided		**0.39**	**0.39**	Not provided		**0.93**	**0.45**	Not provided
95% CI		0.35, 0.64	0.40, 0.72	0.39, 0.65		0.32, 0.78	0.24, 0.67			0.23, 0.67	0.22, 0.68			0.42, 2.03	0.16, 1.24	
p-value		<0.001	<0.001	<0.001		0.002	<0.001			<0.001	<0.001			0.855	0.121	
	DREAM															
N	155		153	153	56		54	54	32		39	39	24		15	15
Rate/year	2.40		1.24	1.24	3.08		1.12	1.12	3.64		1.13	1.13	2.8		1.15	1.15
Rate ratio (mepo/pbo)			**0.52**	**0.52**			**0.36**	**0.36**			**0.31**	**0.31**			**0.41**	**0.41**
95% CI			0.39, 0.69	0.39, 0.69			0.24, 0.55	0.24, 0.55			0.18, 0.53	0.18, 0.53			0.19, 0.86	0.19, 0.86
p-value			<0.001	<0.001			<0.001	<0.001			<0.001	<0.001			0.019	0.019
	SIRIUS															
N	66	69		69	48	54		54	15	22		22	33	32		32
Rate/year	2.12	1.44		1.44	2.1	1.62		1.62	2.16	1.75		1.75	2.05	1.54		1.54
Rate ratio (mepo/pbo)		**0.68**		**0.68**		**0.77**		**0.77**		**0.81**		**0.81**		**0.75**		**0.75**
95% CI		0.47, 0.99		0.47, 0.99		0.51, 1.17		0.51, 1.17		0.40, 1.64		0.40, 1.64		0.44, 1.29		0.44, 1.29
p-value		0.042		0.042		0.222		0.222		0.556		0.556		0.298		0.298
	DREAM & MENSA meta-analysis															
N	346			538	120			197	77			141	43			56
Rate ratio (mepo/pbo)			Not requested	**0.51**			Not requested	**0.41**			Not requested	**0.35**			Not requested	**0.55**
95% CI				0.42, 0.62				0.31, 0.55				0.25, 0.50				0.32, 0.92
p-value				<0.001				<0.001				<0.001				0.023
	DREAM & MENSA & SIRIUS meta-analysis															
N					168			251	92			163	76			88
Rate ratio (mepo/pbo)			Not possible – different covariates				Not requested	**0.50**			Not requested	**0.42**			Not requested	**0.64**
95% CI								0.40, 0.64				0.30, 0.57				0.44, 0.93
p-value								<0.001				<0.001				0.019

Analysis of number of exacerbations performed using a negative binomial model with covariates of treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), region, and baseline % predicted FEV_1, and with logarithm of time on treatment as an offset variable. CI = confidence interval; GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; IV = intravenous; mOCS = maintenance oral corticosteroids; SC = subcutaneous

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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 smaller (61 ml) at 52 weeks than in MENSA (98ml and 100 ml; Table 17); the reason for this is not clear. Data for other DREAM populations, or for other sub-populations and meta-analyses, were not reported in the CS or requested by the ERG (Table 17).

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

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Table 3: Results for pre-bronchodilator FEV_1 (ml)

	ITT				GSK PP				GSK PP excl. stable mOCS				Stable mOCS			
	Placebo	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**	**Placebo**	**Mepo 100mg SC**	**Mepo 75mg IV**	**Mepo 75 or 100mg**
	MENSA															
N	189	192	188	380	59	76	59		40	53	43					
LS mean (SE)	1907 (31.4)	2005 (31.1)	2007 (31.5)	2006 (22.1)	1844 (59.1)	1960 (52.8)	1975 (59.3)		1855 (75.4)	1962 (67.3)	2002 (72.9)					
LS mean change (SE)	86 (31.4)	183 (31.1)	186 (31.5)	184 (22.1)	118 (59.1)	234 (52.8)	249 (59.3)		114 (75.4)	221 (67.3)	261 (72.9)					
Difference (mepo-pbo)		**98**	**100**	**99**		**116**	**131**	Not provided		**107**	**148**	Not provided		Not requested	Not requested	Not requested
95% CI		(11, 184)	(13, 187)	(23, 174)		(-41,272)	(-35,296)			(-95,309)	(-59,355)					
p-value		0.028	0.025	0.010		0.147	0.120			0.295	0.160					
	DREAM															
N	127		129	129												
LS mean (SE)	1942 (37.7)		203 (37.6)	2003 (37.6)												
LS mean change (SE)	60 (37.7)		121 (37.6)	121 (37.6)												
Difference (mepo-pbo)			**61**	**61**			Not provided	Not provided			Not provided	Not provided			Not requested	Not requested
95% CI			(-39, 161)	(-39, 161)												
p-value			0.229	0.229												
	SIRIUS															
N	62	66		66	46	52		52								
LS mean (SE)	1955 (56.5)	2070 (55.1)		2070 (55.1)	1896 (66.2)	2036 (62.3)		2036 (62.3)								
LS mean change (SE)	-4 (56.5)	111 (55.1)		111 (55.1)	17 (66.2)	157 (62.3)		157 (62.3)								
Difference (mepo-pbo)		**114**		**114**		**140**		**140**		Not requested		Not requested		Not requested		Not requested
95% CI		(-42, 271)		(-42, 271)		(-41, 321)		(-41, 321)								
p-value		0.151		0.151		0.129		0.129								
	Meta-analyses not provided in the CS or requested by the ERG															

Analysis performed using mixed model repeated measures with covariates of baseline, region, treatment and visit, plus interaction terms for visit by baseline and visit by treatment group. CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; GSK PP = GlaxoSmithKline proposed population; ITT = intention-to-treat; IV = intravenous; ml = millilitres; mOCS = maintenance oral corticosteroids; SC = subcutaneous; SE = standard error

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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 (n=286, 46% of total) and MENSA (n=245, 43% of total), for patients with 2 exacerbations a threshold of between 350 and 400 cells/ µL and between 100 and 150 cells/ µL, respectively would be required to achieve the specified reduction in rate. For patients with ≥4 exacerbations (representative of the GSK PP) the reported threshold is <50 cells/ µL in DREAM and between 50 and 100 cells/ µL in MENSA.

Table 4: Eosinophil levels that predict a 30% reduction in exacerbations conditional on exacerbations in the previous year (clarification response A15)

Exacerbations in previous year	Eosinophil level that predicts a 30% reduction	
	Study DREAM	Study MENSA
2 exacerbations	Between 350 and 400 cells/ µL	Between 100 and 150 cells/ µL
3 exacerbations	Between 100 and 150 cells/ µL	Between 50 and 100 cells/ µL
≥4 exacerbations	<50 cells/µL	Between 50 and 100 cells/ µL

The rate of exacerbations according to blood eosinophil level in MENSA is shown in Table 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.

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However, the results observed for subgroups based on a threshold of ≥300/µL in the previous 12 months were not intuitive for the following two reasons:

1) Exacerbation rates in the placebo groups were lower for patients with ≥300/µL in the previous 12 months compared with patients with <300/µL (1.64 vs. 1.89), and
2) Patients with ≥300/µL in the previous 12 months had a smaller reduction in exacerbations for mepolizumab vs. placebo (RR=0.69 and 0.57) than patients with <300/µL (RR=0.27 and 0.27), which is not intuitive.

It should be noted that patients with eosinophils <300/µL in the past year would all have had eosinophils ≥150/µL at screening, while patients with ≥300/µL in the past year may or may not have had ≥150/µL at screening. This is due to the MENSA inclusion criteria in which patients were required to have eosinophils ≥150/µL at screening and/or ≥300/µL in the past year. This may partially account for the above findings.

Table 5: Analysis of rate of clinically significant exacerbations by blood eosinophil criteria (MENSA, adapted from CS p103 Table 44)

Blood eosinophil inclusion criteria group	Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
Criterion: ≥300/µL in the previous 12 months			
<300/µL in the previous 12 months			
N Exacerbation rate/year	70 1.89	61 0.51	48 0.50
RR (mepolizumab/placebo) 95% CI		**0.27** 0.15, 0.51	**0.27** 0.14, 0.52
≥300/µL in the previous 12 months			
N Exacerbation rate/year	121 1.64	130 1.13	146 0.94
RR (mepolizumab/placebo) 95% CI		**0.69** 0.49, 0.98	**0.57** 0.41, 0.80
Criterion: ≥150/µL at screening[1]			
<150/µL at screening			
N Exacerbation rate/year	21 1.31	30 1.23	35 1.20
RR (mepolizumab/placebo) 95% CI		**0.94** 0.43, 2.07	**0.91** 0.44, 1.90
≥150/µL at screening			
N Exacerbation rate/year	167 1.75	155 0.81	155 0.67

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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 (in the GSK PP and the subgroup analyses) are defined as exacerbations requiring systemic corticosteroids (or for subjects on mOCS, a two-fold or greater dose increase) and/or hospitalisations or ED visits. This is contrary to the definition supplied in the company's clarification response, but is the definition provided in the Fact Check process.

The CS states that the interaction between the number of previous exacerbations and treatment group was potentially significant (p=0.014); this indicates that there was a potentially significant difference in exacerbation reduction for patients according to the number of prior exacerbations. For patients receiving mepolizumab 75mg, the RRs for exacerbations vs. placebo were 0.86 (2 previous exacerbations); 0.42 (3 previous exacerbations); and 0.36 (4 previous exacerbations). However, although the RRs appear more favourable for subgroups with 3 or ≥4 than for 2 previous exacerbations, there appears to be little difference in RR between those with 3 and ≥4 previous exacerbations (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.

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Table 6: **Analysis of rate of clinically significant exacerbations by previous omalizumab use (ITT population, MENSA, CS Table 48)**

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

CI = confidence interval; IV = intravenous; SC = subcutaneous

4.2.4 Open-label extension studies

4.2.4.1 Description of open-label extension studies

The CS provided data on two open-label, non-randomised, non-controlled extension studies enrolling patients completing the pivotal RCTs (Table 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 or ≥200/µL within 12 months of screening and >300/µL or ≥200/µL at screening.

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Table 7: Open-label extension studies COSMOS and COLUMBA (adapted from CS Tables 74 and 75)

Trial	Intervention	Population	Outcomes	Duration
COSMOS (MEA115661)	• SC Mepolizumab 100mg • Patients previously on mepolizumab continued without interruption; patients previously on placebo started on mepolizumab	• Patients completing MENSA or SIRIUS • Receiving controller medication	Long-term safety and efficacy data	52 weeks (in addition to MENSA or SIRIUS RCT duration of 32 or 24 weeks)
COLUMBA (MEA115666)	• SC Mepolizumab 100mg • Cessation and re-start of mepolizumab with ≥12 month treatment break • Treatment for up to 3.5 years	• Patients having received ≥2 doses study drug in DREAM • Receiving controller medication	Long-term safety and efficacy data	Up to 3.5 years (following ≥12 month treatment break after 52 week DREAM trial)

SC = subcutaneous

A total of 998 patients have been enrolled in COSMOS (N=651) and COLUMBA (N=347; Table 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 (525/576, 91%) and SIRIUS (126/135, 93%) elected to continue treatment and directly rolled over into COSMOS. All patients received mepolizumab 100mg SC in the open-label extension regardless of their treatment assignment in the double-blind parent study. COLUMBA started before COSMOS, thus patients have longer treatment exposure in this study. As of the February 28th, 2014 data cut-off date for the interim analysis, 96% of patients were continuing treatment and there were 643 patient years of exposure. The most common reasons for premature withdrawal from the open-label studies were AEs and withdrawal of consent (1% for each). The As Treated (AT) population consisted of all subjects who received at least one dose of mepolizumab; this represents the primary population for all summaries of efficacy and safety measures.

The demographics for patients in COSMOS and COLUMBA were similar to those of the RCTs from which patients enrolled (Table 32).

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Table 8: Patient numbers in open-label extension studies COSMOS and COLUMBA (CS p153-4)

	Receiving mepolizumab 100mg SC	
Trial	**COLUMBA (interim)**	**COSMOS (final)**
% enrolling from RCTs	From DREAM: 347/616 (56%)	From MENSA: 525/576 (91%) From SIRIUS: 126/135 (93%)
Previous treatment		Previous mepolizumab: 414 Previous placebo: 237
N enrolled	**347**	**651**
Withdrawn	22 (6%)	66 (10%)
Continuing treatment (interim)	325 (94%)	N/A
Completed	N/A	585 (90%)
Primary reason for withdrawal, N (%):		
Adverse event	8 (2)	11(2)
Withdrew consent	8 (2)	14 (2)
Lack of efficacy	0	19 (3)
Protocol deviation	2 (<1)	8 (1)
Physician decision	1 (<1)	9 (1)
Lost to follow-up	2 (<1)	3 (<1)
Met protocol stopping criteria	1 (<1)	2 (<1)

SC = subcutaneous

Table 9: Demographics for COSMOS and COLUMBA, ITT populations (CS p152-3)

Demographic	COLUMBA (N=347)	COSMOS (N=651)
Age, yr Mean (SD)	52.2 (10.7)	51.1 (13.9)
Gender, (%) Female	65	55
Race, (%) White	92	81
Body Mass Index, kg/m^2 Mean (SD)	28.62 (6.10)	28.02 (5.85)

SD = standard deviation

4.2.4.2 Clinical effectiveness results of open-label extension studies COSMOS and COLUMBA

Rate of exacerbations

The rate of exacerbations per year in COLUMBA was 0.67 (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.

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4.2.5 Safety of mepolizumab

The CS provided a review of safety evidence and AEs for mepolizumab. Results were presented for the placebo-controlled trials (DREAM, MENSA and SIRIUS) and the non-randomised, non-controlled, open-label extension studies (COSMOS and COLUMBA). Data collection has been completed for COSMOS but is ongoing for COLUMBA (data cut-off of 28th February 2014). The CS provided safety data collated across the three RCTs. The ERG requested additional data on AEs of special interest; these were provided by the company for each trial separately (clarification response Question A12) and collated across trials by the ERG.

4.2.5.1 Rates of AEs

AEs with relative risk of 1.5 or greater for mepolizumab vs. placebo in RCTs: AEs for which the risk was at least 1.5 times as great for mepolizumab vs. placebo are shown in Table 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 10: Adverse events with relative risk of 1.5 or greater for mepolizumab vs. placebo for DREAM, MENSA and SIRIUS (adapted from CS Table 89)

Event	Treatment	N	Number (%) with Event		Adjusted Cumulative Proportion [1]	Relative Risk	(95% CI) [2]
Eczema	Placebo	412	2	0.50%	0.50%		
	All Doses	915	23	2.50%	2.60%	5.34	(1.25, 22.78)
Nasal congestion	Placebo	412	4	1.00%	1.00%		
	All Doses	915	24	2.60%	2.50%	2.62	(0.89, 7.72)
Dyspnoea	Placebo	412	4	1.00%	1.10%		
	All Doses	915	23	2.50%	2.30%	2.2	(0.78, 6.20)
Rhinitis allergic	Placebo	412	7	1.70%	1.70%		
	All Doses	915	27	3.00%	2.80%	1.64	(0.70, 3.85)
Urinary tract infection	Placebo	412	9	2.20%	2.10%		
	All Doses	915	32	3.50%	3.40%	1.63	(0.77, 3.47)

[1] Adjusted using Cochran-Mantel-Haenszel weights [2] Calculated using the Cochran-Mantel-Haenszel method. CI = confidence interval

AEs with a frequency of 5% or greater for mepolizumab in RCTs: AEs with a frequency of ≥5% for mepolizumab are shown in 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.

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The ERG notes that the longest follow-up for which data are provided for mepolizumab 100mg SC is 84 weeks (in MENSA then COSMOS) although eventually data for up to 3.5 years will be available from COLUMBA. Given that treatment might be expected to be life-long, there is therefore uncertainty regarding the long-term safety of mepolizumab.

4.2.5.7 Summary of safety data

Mepolizumab appears to be generally well-tolerated in severe eosinophilic asthma patients, with the exception of possible increased risks of eczema, nasal congestion, dyspnoea and injection site reactions with mepolizumab. Hypersensitivity reactions, infections and malignancy occurred at similar rates with mepolizumab and placebo. Cardiac events occurred at similar rates with mepolizumab and placebo, whilst rates of serious cardiac events and serious CVT events were slightly higher for mepolizumab (though event rates were low). In terms of SAEs, there were two cases each of herpes zoster, hypertension and myocardial ischaemia for mepolizumab, versus none for placebo.

In both the placebo-controlled trials and open-label studies, 5%-6% of patients treated with mepolizumab 100mg SC developed anti-mepolizumab antibodies. There is also no evidence for the long-term safety of mepolizumab 100mg SC beyond 84 weeks (in MENSA then COSMOS) although eventually data for up to 3.5 years will be available from COLUMBA.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Omalizumab is a relevant comparator for patients who exhibit both allergic (IgE) and eosinophilic phenotypes of severe asthma and who would be potentially eligible for either medication. As there are no head-to-head trials comparing mepolizumab and omalizumab, the company undertook a network meta-analysis (NMA) to compare the two treatments indirectly by synthesising trials comparing either drug to a common comparator, standard of care (CS Section 4.10 p127-149).

Search strategy for NMA

The CS reports a literature search for studies of both mepolizumab and omalizumab (described in Section 4.1). The ERG considers the search strategy to be appropriate and would expect it to identify relevant studies of mepolizumab and omalizumab.

Study selection criteria for NMA

The inclusion and exclusion criteria for the NMA are not very clearly laid out in the CS and so are summarised below by the ERG.

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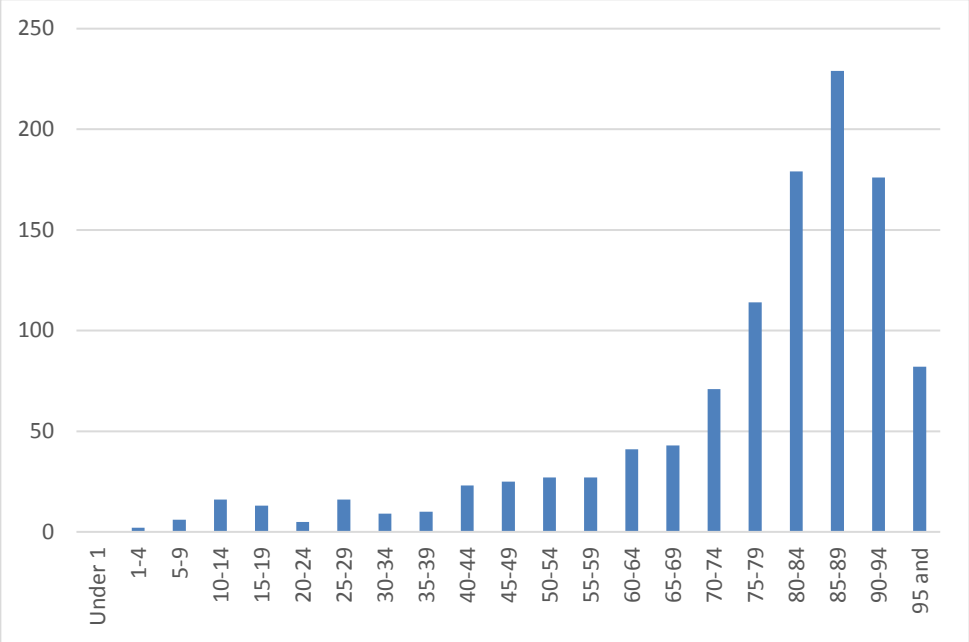
Figure 11 shows the deaths caused by asthma registered in England and Wales in 2014 stratified by age as reported by the Office for National Statistics.[48] These data confirm that asthma-related mortality increases markedly after the age of 65 years with 80% of the asthma-related deaths occurring in people aged 65 years or older.

Figure 1: Asthma deaths in England and Wales, 2014. Source: Office for National Statistics[48]



The NRAD report analyses 195 asthma-related deaths. The categories of locations of death within the NRAD report were: home (private address) 41%; hospital, arrest in hospital 30%; hospital, pre-hospital arrest 23%; nursing / residential home 3%; holiday 2%; and other 1%.

The company's model assumes that all deaths in Watson *et al*. would be categorised as 'hospital, arrest in hospital', which account for the 30% of deaths in the NRAD report, and that therefore the total number of deaths would be 100/30 times greater than those reported in Watson *et al*. These additional deaths were divided between those exacerbations that required an ED visit (23/70) and those assumed to only require an OCS burst (47/70). The distribution of deaths amongst the three groups of exacerbations: hospitalisation; ED visit and OCS burst were assumed constant and independent of the number of deaths reported in hospital. The ERG notes that should any of the deaths in Watson *et al*. be assignable to the 'hospital, pre-hospital arrest' category, then the number of deaths due to asthma exacerbations would be overestimated. However, this is unlikely as it appears that all deaths were reported after admission.

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5.2.11.3 Scenario analysis: OCS sparing

The company performed a scenario analysis that attempted to include long-term costs and consequences of maintenance OCS. For that purpose, the company undertook a study using the Clinical Practice Research Datalink (CPRD) to estimate the dose-dependent risk of developing 6 AEs associated with systemic corticosteroid therapy: myocardial infarction; glaucoma; diabetes; cataracts; osteoporosis; and peptic ulcer.

The company used the data collected during SIRIUS to calculate the reduction in OCS use in two ways: using the percentage of patients that managed a total reduction of OCS and the median percentage of OCS reduction. The company stated that the median was used instead of the mean due to the skewedness of the distribution, although the ERG notes that it is typical to use mean values in economic evaluations. The ERG notes that using the percentage of patients that had managed to discontinue OCS treatment was likely to underestimate the OCS dose reduction. The ERG considers that it would have been more appropriate to use population-dependent data instead of assuming that the reductions in OCS use and the proportion of patients on mOCS in the ITT population was applicable for all three populations. The company assumes that the OCS reduction data gathered in SIRIUS are applicable for omalizumab. The ERG notes that data relating to the proportion of patients discontinuing OCS are available in the Assessment Group's report for the omalizumab MTA and are markedly different from those for mepolizumab: 14.5% of patients discontinued OCS treatment in SIRIUS compared with 32.2% of omalizumab patients who were on baseline mOCS in the EXALT trial.[45] However, a direct comparison of discontinuation percentages from the open label EXALT study and SIRIUS has to be taken with caution.

The time horizon used to calculate the costs and consequences of AEs associated with systemic OCS was 10 years, matching the biologic treatment duration in the base case analysis. The ERG notes the use of a time horizon shorter than lifetime is likely to underestimate the benefits of OCS sparing, as some of the diseases avoided during the treatment are chronic and therefore would have been suffered by the patients for the rest of their lives, or these diseases could develop or become symptomatic beyond the 10-year time horizon.

The company uses data from MENSA to calculate exacerbation rates in mepolizumab patients in addition to using the OCS usage reduction data from SIRIUS. The ERG notes that this, in isolation, is likely to overestimate the aggregate benefits of mepolizumab, as exacerbation rates might not decrease as much when reducing OCS usage.

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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 11: Results of the subgroup analysis for mOCS users with a blood eosinophil count of ≥150 cells/µL at initiation of treatment and <4 exacerbations

	Total Cost	Δ Cost	Total QALY	Δ QALY	ICER (vs.)
Mepolizumab + Standard of Care	[redacted]	-	[redacted]		
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	£78,716

The ERG was also concerned that the age stratification of asthma related mortality rates in Watson *et al*.[1] could lead to an overestimation of deaths due to asthma in the early years within the model. In reply to the ERG's clarification letter, the company performed two exploratory analyses which the company stated should be interpreted with caution. These were combining the asthma-related mortality rates reported by Watson *et al*.[1] and Roberts *et al*.,[2] using two different approaches: by applying the rate ratios derived from comparing the rate for the 35-44 age band with the other age bands as reported by Roberts *et al*. to the mortality rate reported by Watson *et al*. for the 17-44 age band (option 1); and assuming the same number of exacerbations across the three age bands and fitting the total deaths reported by Watson *et al*. in a way that the relative RRs of the different age bands were similar to those reported by Roberts *et al*. (option 2). The ERG preferred option 2: the resultant assumed mortality rates using this approach are shown in Table 66.

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Table 12 Mortality rates calculated based on the number of deaths and hospitalizations reported for the ≥45 group in Watson *et al.*[1] and the ratios in Roberts *et al.*[2] (option 2)

Age group	Roberts *et al.*[2]		Watson *et al.*[1]			Watson *et al.*[1] + Roberts *et al.*[2]			
	p	ratio	p	n	N	p	ratio	n	N
45-54	0.0045		0.0248	177	7143	0.0076		18	2381
55-64	0.0127	2.84				0.0214	2.83	51	2381
≥65	0.0278	6.20				0.0454	6.00	108	2381

The ERG considers that the exacerbation rates used in the model for patients who meet the continuation criteria could be inappropriate: these rates were measured in the MENSA trial shortly after the beginning of the treatment, based on a 16-week time span and therefore might not be representative of the long-term effectiveness of mepolizumab and may be affected by seasonality; further, there may be a regression to the mean. In contrast, in the COSMOS study, the rates were measured in a period of a full year in patients that had already been on mepolizumab for 32 weeks. The company acknowledged in their clarification responses (question A19) that the continuation criteria in COSMOS were consistent with recommendations in the SmPC. Additionally, the percentage of MENSA patients that went on to participate in COSMOS is almost identical to those meeting the continuation criteria in the ITT population of MENSA (90.1% vs 90.9%). For these reasons, during the clarification process, the ERG requested the company to undertake an analysis whereby exacerbation rates from COSMOS were used in the model as exacerbation rates for patients on mepolizumab who met the continuation criteria (question B4). However, the company did not undertake the requested analysis and argued instead that the exacerbation rate measured in COSMOS in patients who had been treated with mepolizumab during MENSA (rate=0.9) was similar to that measured in the ITT population in MENSA (rate=0.877). The ERG agreed in the similarity of these two rates but note that they are markedly different to the rate used in the model for patients on mepolizumab meeting the continuation criteria (rate=0.55 in the ITT population).

The ERG also requested a scenario analysis based on the exacerbation rates and utilities recorded in the DREAM trial and analyses where exacerbation rates were calculated through a meta-analysis of data gathered in MENSA and DREAM, both using EQ-5D utilities (DREAM) and the SGRQ-mapped utilities (MENSA). The results of this request were provided to the ERG within the company response.

The ERG believes that the results of the SIRIUS trial are particularly relevant, since it assesses the effectiveness of mepolizumab in patients on mOCS. The GINA guidelines[58] specify that "patients with persistent symptoms or exacerbations despite correct inhaler technique and good adherence with Step 4 treatment and in whom other controller options have been considered" should be considered in Step 5, which usually entails maintenance OCS. Bousquet *et al.* consider that having more than two exacerbations in a year is sufficient for asthma to be categorised as "poorly controlled".[59] Considering that the patients in the GSK PP that are not on maintenance

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OCS suffered at least four such exacerbations in the previous year, the ERG believes that the inclusion of mOCS for these patients should have been considered. Therefore, the ERG believes that mOCS is a potentially relevant comparator for the GSK PP in addition to the comparator of usual Step 4 treatment and that the SIRIUS trial is representative of this comparison. Consequently, the ERG requested analyses based on the exacerbation rates and utilities recorded in SIRIUS, but the company claimed there was no time within the STA process to perform a full reanalysis and undertook a scenario analysis where utilities estimated from SGRQs gathered in SIRIUS were used while using the exacerbation rates from MENSA. The company did not report results for the GSK PP excl. stable mOCS claiming that there were too few patients in this sub-population in SIRIUS.

Table 13: Utilities measured in SIRIUS and used in the company's exploratory analysis

	Full Trial Population (ITT from SIRIUS)	GSK PP excl. stable mOCS	GSK PP
	Mean (SE)	Mean (SE)	Mean (SE)
Add-on mepolizumab: All patients	0.710 (0.027)	N/A	0.711 (0.028)
SoC	0.706 (0.026)	N/A	0.718 (0.029)
Add-on mepolizumab: Meeting CC	0.716 (0.029)	N/A	0.696 (0.036))

SoC: Standard of care; CC: continuation criteria

The ERG consider that the continuation criteria proposed by the company (i.e. continue on treatment unless the exacerbation rate increases) imply that a subgroup of patients could remain on treatment even when experiencing no improvement. The ERG requested that the company present exploratory analyses to assess the impact on the ICER of the amending the continuation criteria such that patients had to improve by a certain amount (as gauged by reduction of exacerbations or OCS use). The company replied that it did "not believe it is appropriate" to quantify the level of improvement in terms of reduction of exacerbations because for patients "on maintenance OCS, who may be less likely to experience a further reduction in exacerbations", mepolizumab "provides the opportunity to reduce OCS exposure". However, in response to this request, the company reported results of exploratory analyses varying both the percentage of patients meeting the continuation criteria and the time to continuation assessment. The ERG noted that the validity of these exploratory analyses was

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The ERG would have preferred a base case analysis that was not restricted by the blood eosinophil count at screening but which still maintained a requirement for four or more exacerbations. However, the ERG did not have access to the necessary data and did not request these data or the corresponding analysis to be undertaken by the company as part of the clarification process. As such, the exploratory analyses presented in this section do not fully represent the true ERG base case.

The ERG modified some of the settings of the company's base case analysis for its analyses. The exploratory analyses include the following amendments:

1) Use of directly measured EQ-5D scores instead of the scores mapped from SGRQ (therefore adhering to the NICE Reference Case and the preference of the Appraisal Committee in the omalizumab MTA);
2) Use of asthma-related mortality rates estimated by the company combining the data from Watson *et al.*[1] and Roberts *et al.*[2] in response to the ERG's clarification questions (described as Option 2 in Section 5.2.11.4);
3) Based on feedback from the clinical experts to the ERG, assuming that a stopping rule of 10 years was inappropriate and that no fixed stopping rule would be applied;
4) Using the average length of the exacerbations measured in MENSA (12.68, 10.41, and 20.70 days for exacerbations requiring OCS burst, ED visit, and hospitalisation respectively) instead of the time over which EQ-5D was captured in Lloyd *et al*. [51] (28 days);
5) Setting the exacerbation rates for those meeting the continuation criteria to those observed in the COSMOS study. However, the ERG did not have access to the exacerbation rates for the GSK PP and GSK PP excl. stable mOCS in COSMOS. In order to overcome this limitation, the ERG estimated these rates based on the exacerbation rate measured in COSMOS in patients that had been on mepolizumab during MENSA, as reported in the company's clarification response (rate=0.90). The ERG estimated the rates for the GSK PP and GSK PP excl. stable mOCS by multiplying this rate by the RRs between rates of the ITT population and GSK PP and GSK PP excl. stable mOCS as used in the base case. The resulting rates are shown in Table 69.

Table 14: Exacerbation rates for patients on mepolizumab after continuation assessment based on COSMOS

	ITT		GSK PP excl. stable mOCS		GSK PP	
	Annual rate	4-weekly rate	Annual rate	4-weekly rate	Annual rate	4-weekly rate
Base case	0.550	0.042	0.723	0.056	0.645	0.050
COSMOS	0.900	0.069	1.183†	0.091	1.054‡	0.081

† 0.9*(0.723/0.550)
‡ 0.9*(0.645/0.550)

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Table 15: Results of the exploratory analyses undertaken by the ERG

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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)															

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	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

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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 16: Results for the stable mOCS population based on the ERG's base case analysis

	Total Cost (£)	Δ Cost (£)	Total QALY	Δ QALY	ICER (£)
Mepolizumab + standard of care	[redacted]		[redacted]		
Standard of care	[redacted]	[redacted]	[redacted]	[redacted]	167,778

The ERG performed exploratory analyses using data collected in the SIRIUS trial combined with scenario numbers 2-5 in Table 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].

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Table 17: Result of the exploratory analyses based on SIRIUS*

	ITT					GSK PP				
	Total cost (£)	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (£)**	**Total cost (£)**	**Δ Costs (£)**	**Total QALYs**	**Δ QALYs**	**ICER (£)**
ERG's base case + utilities and exacerbation rates from SIRIUS (population-specific utilities)										
Mepo	[redacted]		[redacted]			[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. The ERG comment that if there has been an increase in drug costs for mepolizumab (based on changes in weight and baseline IgE levels) without an increase in effectiveness then including Scenario A would be unfavourable to mepolizumab. For completeness the estimated ICER of mepolizumab compared with SoC calculated from the NMA is also shown in Table 74.

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Table 18: Results of exploratory analyses ERG omalizumab

Scenario Number		Mepo	Omalizumab	Mepo vs. omalizumab	SoC	Mepo vs. SoC
	Deterministic results incorporating scenario numbers 1-5 from Table 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

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