NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Mepolizumab for treating severe eosinophilic asthma [ID798]

The following documents are made available to the consultees and commentators:

1. **Comments on the Appraisal Consultation Document** from **GlaxoSmithKline**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Asthma UK
   - British Association of Dermatologists
   - British Thoracic Society
   - Novartis

3. **Comments on the Appraisal Consultation Document from experts:**
   - Professor Andrew Wardlaw

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **ERG critique of company's response to the ACD**

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

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

Company response to ACD

25th April 2016

1 Are the recommendations sound and a suitable basis for guidance to the NHS?

Patients with severe eosinophilic asthma, which is refractory to other treatments, have significant unmet clinical need for alternative treatments. Mepolizumab is the first targeted therapy for patients with an eosinophilic phenotype. Mepolizumab has clearly demonstrated effectiveness in reducing exacerbations and dependency on daily oral corticosteroids (OCS), and improving symptoms.

GSK does not agree that the current recommendations are sound and represent a suitable basis for guidance to the NHS.

Having heard the concerns of the committee, GSK is proposing a revised population, in patients who:

- *have been diagnosed with severe refractory eosinophilic asthma,*
- *and need continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)*
- *and have a blood eosinophil count of ≥300 cells/μL in the last year'*

We will present new evidence of the clinical and cost effectiveness in this revised population.

We have laid out the key areas within the recommendations that should be taken into consideration, and are discussed in detail in our response:

1. **The committee concluded that the population for guidance should include a criterion for maintenance OCS based on their interpretation of the marketing authorisation and the term 'refractory'**. However, mepolizumab is indicated as an add-on treatment for severe refractory eosinophilic asthma (SREA) in adult patients. This licensed population includes patients who take maintenance oral corticosteroids (OCS) or patients who require several courses of OCS during the year. Limiting mepolizumab to maintenance OCS patients does not address the latter group which also has severe refractory disease and would benefit from the medicine. *(See section 1.1 and 1.2 of this response)*
2. **We agree with the committee's position that a sub-group population for guidance has to be clinically plausible. We believe that a suitable sub-group can be identified and that exacerbation history and blood eosinophils are relevant parameters to use, based on our clinical data**.

   Exacerbation history *(See section 1.3)*

   - A clinically plausible subgroup of diagnosed SREA patients can be identified by a baseline exacerbation rate of ≥4 exacerbations in the last year despite receiving high dose ICS, plus at least one additional controller.
   - GSK agrees that eosinophilic patients with ≥2 exacerbations in the previous year clearly benefit from add on mepolizumab therapy as shown in our clinical trials. However, as a sub-population, patients with a higher baseline exacerbation rate (≥4 in the previous year) have a higher burden of disease. This aligns with clinical opinion, selecting patients with an increased disease burden and greater potential to benefit from mepolizumab treatment.
   - The British Thoracic Society has shown in a study of the BTS Difficult Asthma Registry that severe asthma patients with a median 4 OCS courses per year suffer from *'substantial excess morbidity from multiple diseases and adverse effects associated with systemic corticosteroid exposure'* (e.g. osteoporosis, osteopenia, cardiovascular disease and glaucoma, obesity, psychiatric disorders, dyspeptic symptoms and hypertension) (1). BTS/SIGN highlights that *'Patients on long-term steroid tablets (for*

example, longer than three months) or requiring frequent courses of steroid tablets (for example, three to four per year) will be at risk of systemic side effects.' Therefore, providing mepolizumab to this patient population will reduce exposure to harmful levels of OCS.

- Existing NICE guidance in a different severe asthma population recommends limiting use to '*continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)'.* This is equivalent to defining a population by exacerbation history, as an exacerbation would require at least a course of oral corticosteroids. Therefore, ≥4 exacerbations (frequent treatment with ≥4 courses of OCS) in the last year is already used in clinical practice.

Eosinophils *(See section 1.4)*

- Mepolizumab is a medicine specifically designed to treat eosinophilic asthma. From our clinical trials, specific blood eosinophil levels were the key marker in terms of identifying patients likely, and unlikely, to respond to treatment (threshold counts provide both positive and negative predictive value).
- Our data shows that with increasing blood eosinophil levels, disease burden increases and response to mepolizumab treatment also increases. A recent meta-analysis shows that exacerbation reduction with mepolizumab compared with placebo based on a threshold >150, >300, >400 and >500 was 52% 59%, 66%, 70% respectively (2).
- The ERG's comment that the effectiveness was '*greater with a blood eosinophil count of less than 300 cells/µL compared with those with ≥300 cells/µL was counterintuitive*', we believe was due to a misunderstanding of our data and is incorrect. Further details are found in response in question 3.
- The European Medicines Agency statement that, blood eosinophil levels were not sufficiently predictive to include a cut off within the marketing authorisation, reflects the difficulty in identifying a specific cut off below which mepolizumab is not effective. However, in the context of NICE guidance it is appropriate to use eosinophil levels to reflect a more severe population which has an enhanced capacity for clinical benefit.
- GSK accepts that a treatment eligibility baseline blood eosinophil level of ≥150 cells/µl may not be intuitive to many clinicians, since predictive biomarker thresholds are an evolving field in patients with SREA. Current feedback from UK clinicians proposes a threshold to select patients for mepolizumab treatment based on a higher eosinophil threshold of ≥300 cells/µl in the past year. This would also address concerns regarding fluctuation in eosinophil levels as the level could be taken any time in the previous year.

Therefore GSK's proposed population is patients who:

- *have been diagnosed with severe refractory eosinophilic asthma,*
- *and need continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)*
- *and have a blood eosinophil count of ≥300 cells/µL in the last year'*

In agreement with NICE, we will present new evidence of the clinical and cost effectiveness in this revised population in section 2.

3. **GSK is concerned with the rejection of the comparison with omalizumab, and the exclusion of previous omalizumab users from mepolizumab guidance**. Whilst we agree that there is only a small overlap population in the UK ([redacted]), the evidence proves that these patients do exist. We acknowledge that in the absence of head to head clinical studies, an indirect comparison analysis is uncertain. This is inevitable given the lack of availability to GSK of patient level data for omalizumab. The Network Meta-Analysis (NMA) does suggest mepolizumab to be more effective. In addition, based on current estimates of usage in clinical practice mepolizumab is also likely to be a less expensive option. Lastly, data from

clinical studies are provided demonstrating that robust effectiveness is also seen in the sub-set of patients previously treated with omalizumab. (*See section 1.5)*

4. **The economic analyses, and many of the underlying assumptions suggested by the committee, are overly conservative and are likely to significantly underestimate the cost effectiveness of mepolizumab compared with standard of care (SoC).**
   We will address the assumptions in more detail in section 1.6, however the key areas of concern include:

- The use of exacerbation data from the COSMOS open label extension study for mepolizumab (which are now available for the committee) without also correcting for the standard of care arm.
- The use of EQ-5D utility values in the model due to substantial ceiling effects in this population (data from DREAM) and the fact that EQ-5D is not available in the key Phase III trial (MENSA).
- The proposed age adjustments, specifically the use of age adjusting Watson for the source of asthma-related mortality following a hospitalisation.

Utilising appropriate assumption mepolizumab provides a cost effective treatment option for severe refractory eosinophilic asthma patients.

1.1 *Appropriate diagnosis and treatment*

The GSK population proposed for reimbursement defines a subgroup of patients within the approved market authorization. This limited subgroup includes only patients diagnosed with severe eosinophilic asthma, and in whom there is expected to be an enhanced potential to benefit from treatment. The market authorization recognizes that clinicians expert in the care of patients with severe asthma can identify this target population (SmPC, 4.2): '*Nucala should be prescribed by physicians experienced in the diagnosis and treatment of severe refractory eosinophilic asthma'*. The committee will be aware that this population suffers considerable morbidity and ill health and utilizes considerable health care costs.

NHS England commissions severe asthma services that have expertise and extensive experience in phenotyping asthma. A diagnosis of severe refractory eosinophilic asthma is a requirement before patients should be considered eligible for add-on mepolizumab treatment (Figure 1).

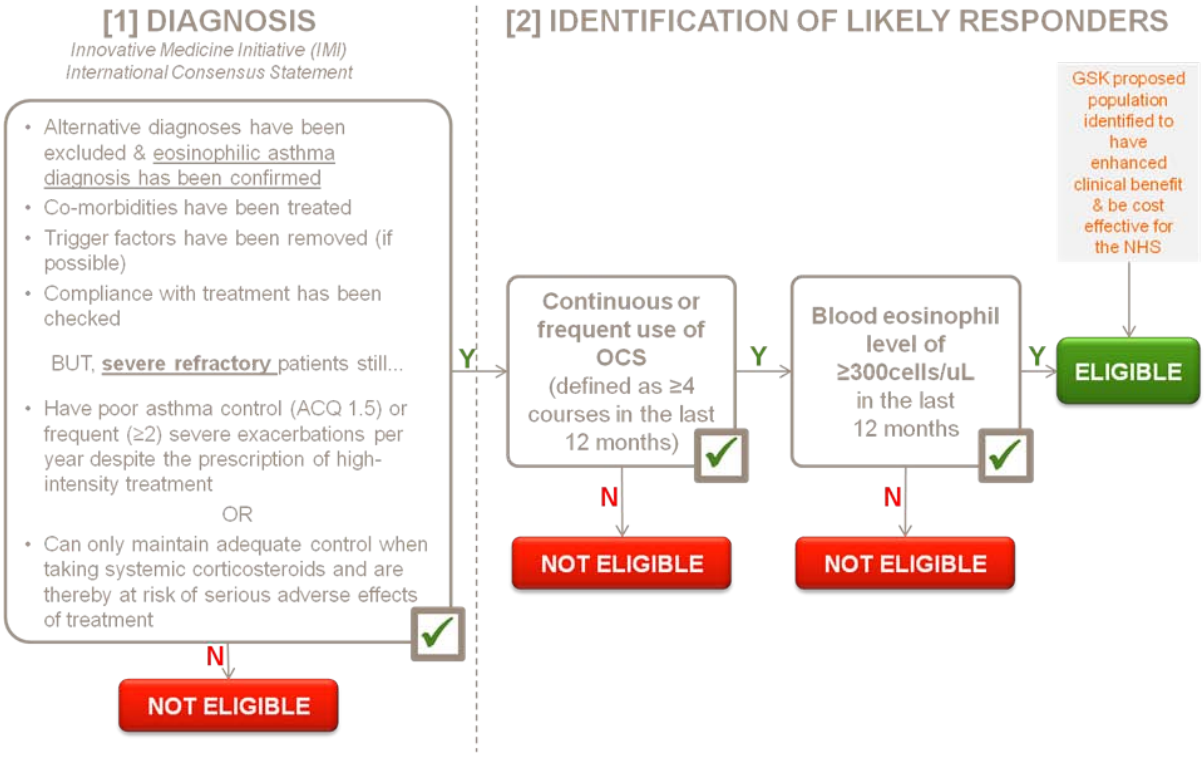
<u>We suggest the following guidance to help physicians indentify patients eligible for mepolizumab:</u>

'Who can have mepolizumab?

You should be able to have mepolizumab if you:

- *have been diagnosed with severe refractory eosinophilic asthma,*
- *and need continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)*
- *and have a blood eosinophil count of ≥300 cells/µL in the last year'.*

Figure 1 Identification of SREA patients eligible for mepolizumab add-on therapy



This section will further discuss the rational for this population (see 1.2, 1.3, 1.4).

1.2 *Maintenance OCS use / Intermittent OCS use*

The current ACD incorrectly does not take into account patients requiring frequent OCS treatment for exacerbations, and therefore does not represent suitable guidance for the NHS (section 4.2 of ACD).

This is not in line with the marketing authorisation nor with current guidelines for the management of asthma.The Innovative Medicine Initiative defines severe refractory asthma as a term that: *'…should be reserved for patients with asthma in whom alternative diagnoses have been excluded, comorbidities have been treated, trigger factors have been removed (if possible) and compliance with treatment has been checked but still have poor asthma control [ACQ 1.5] or frequent (≥2) severe exacerbations per year despite the prescription of high-intensity treatment* ***or*** *can only maintain adequate control when taking systemic corticosteroids and are thereby at risk of serious adverse effects of treatment.' (3)*

This International Consensus Statement supports the mepolizumab EU marketing authorisation (and clinical trial results), in defining mepolizumab-eligible patients as being on frequent or continuous OCS (i.e. uncontrolled at step 4, moving into step 5) or at step 5 of the BTS/SIGN treatment guideline) (Figure 2). In fact BTS/SIGN highlight at step 5 that *'Patients on long-term steroid tablets (for example, longer than three months) or requiring frequent courses of steroid tablets (for example, three to four per year) will be at risk of systemic side effects*.' Thus, mepolizumab is a step 5 therapy and patients are eligible if they fail step 4 of the BTS/SIGN guidelines.

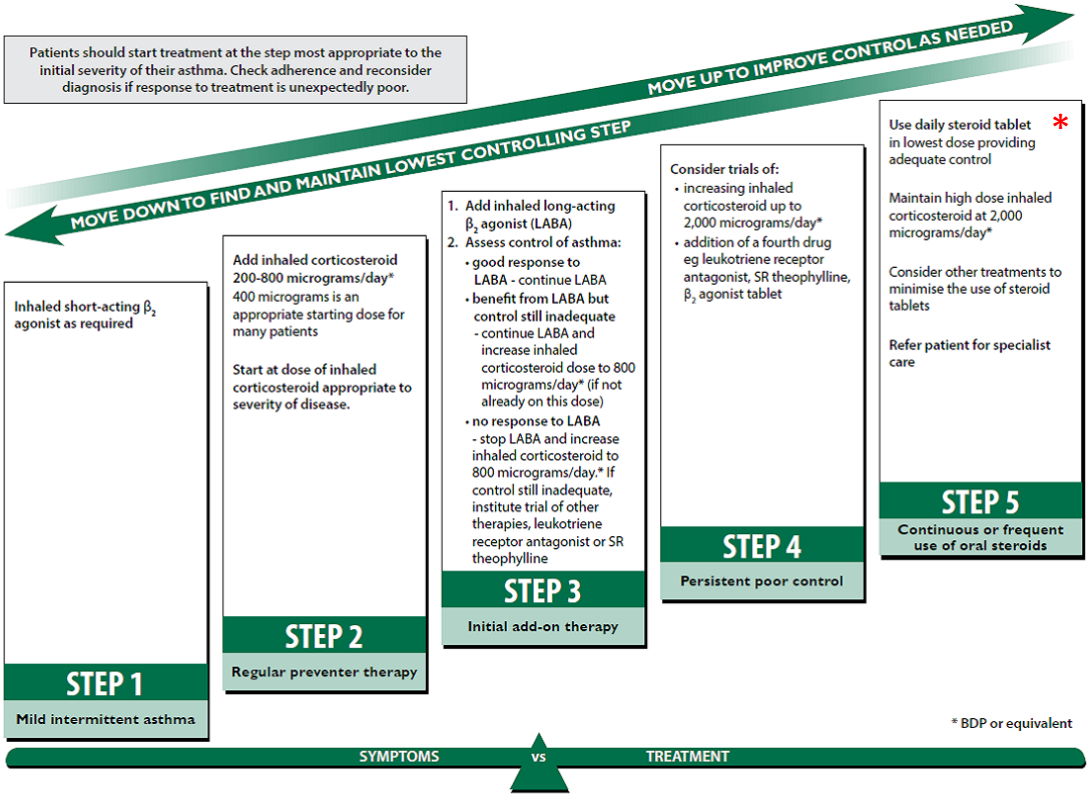
GSK has successfully completed MHRA pre-vetting and is currently marketing mepolizumab for both patient groups on frequent courses and continuous OCS. This includes the entire ITT population of all three RCTs (MENSA, DREAM and SIRIUS). In the three trials all patients had to be on optimised SOC (high dose ICS + additional controller) and for the exacerbation studies DREAM and MENSA a dependence on maintenance OCS was not a requirement (31% and 24% of patients were on maintenance OCS in these 2 studies, respectively).

As a result we respectfully question the committee's conclusion that the most appropriate evidence to inform the appraisal is from the SIRIUS study. The most relevant evidence would actually be the MENSA study supported by appropriate patients from the DREAM study. SIRIUS data should also be considered when relevant to measure the impact of reducing the level of maintenance corticosteroids. All three trials are featured in the SmPC (section 5.1).

As such, GSK considers it inappropriate and inconsistent with our approved market authorization to restrict mepolizumab to only patients receiving maintenance OCS. Such a restriction would significantly disadvantage eligible patients with severe asthma and likely increase the well known and significant problems associated with prolonged steroid use.

In conclusion, we propose that the guidance should include patients needing either continuous or frequent course of corticosteroids as a Step 5 medicine (see Figure 1 and Figure 2).

Figure 2 Proposed population as per the BTS/SIGN guidelines



* **includes '*...patients on long-term steroid tablets (for example, longer than three months) or requiring frequent courses of steroid tablets (for example, three to four per year) will be at risk of systemic side effects significant side effects* from frequent courses...'**

1.3 *Exacerbation History*

We believe the use of exacerbation history (which is associated with the use of frequent courses of oral steroids) is a reasonable and clinically valid approach to identify a target population.

The committee concluded that a criterion based on 4 exacerbations was not clinically appropriate (Section 4.5):-'*because exacerbations are infrequent events, event rates would vary between one year and the next, so defining a criterion on a specific value, may not be reliable (that is, the same patient may experience 3 exacerbations one year, and 4 the next)'*. The ACD states that a population with '*2 or more exacerbations in the previous year*' would be preferred (section 4.6 and 4.21).

GSK agrees that eosinophilic patients with ≥2 exacerbations in the previous year clearly benefit from add on mepolizumab therapy as shown in our clinical trials. However, as a sub-population, patients

with a higher baseline exacerbation rate (≥4 in the previous year) have a higher burden of disease. We agree that severe asthma patients with a median 4 OCS courses per year suffer from '*substantial excess morbidity from multiple diseases and adverse effects associated with systemic corticosteroid exposure*' (e.g. osteoporosis, osteopenia, cardiovascular disease and glaucoma, obesity, psychiatric disorders, dyspeptic symptoms and hypertension) (Sweeney et al 2016). In a different severe asthma population, this increased burden of disease with the identification of ≥4 exacerbations at baseline per year is acknowledged in the NICE omalizumab guidance (TA278) which has a requirement for continuous or frequent treatment with OCS, defined as ≥4 courses of OCS in the previous year. Given severity and that an exacerbation requires the use of OCS, this is equivalent to guidance restricting on the basis of 4 numbers of exacerbations or dependency on maintenance OCS. As clinicians already implement this guidance as part of routine clinical practice when prescribing omalizumab, we would argue that this further supports the clinical plausibility of this restriction.

Patients' higher baseline exacerbation rate allows for a more clinically impactful absolute reduction in exacerbations per year i.e. a greater potential to benefit from add-on mepolizumab treatment. While the rate ratios were broadly the same for subjects with ≥2, ≥3 or ≥4 exacerbations at baseline (Table 1 Analysis of Rate of Clinically Significant Exacerbations by Previous Exacerbations (MENSA, ITT Population), subjects with a higher historic exacerbation rate showed a higher absolute (numerical) reduction of exacerbations per annum which therefore translate into improved cost effectiveness.

Table 1 Analysis of Rate of Clinically Significant Exacerbations by Previous Exacerbations (MENSA, ITT Population)

Baseline Exacerbation Rate in Previous Year	**Rate ratio for exacerbations (95% CI) Percentage reduction**	
	75mg IV	**100mg SC**
>=2 exacerbations (ITT)	0.53 (0.40, 0.72) **47%**	0.47 (0.35, 0.64) **53%**
>= 3 exacerbations	0.51 (0.36, 0.73) **49%**	0.44 (0.31, 0.62) **56%**
>= 4 exacerbations	0.40 (0.25, 0.64) **60%**	0.44 (0.29, 0.69) **56%**

In addition, both the ERG and the clinical advisors to the ERG supported ≥4 exacerbations at baseline as a valid threshold for guidance. From the discussion it also appeared that this threshold was further supported by clinicians on the day of the ACM.

We therefore conclude that the use of exacerbation history (which could also be expressed as the number of courses of OCS required in the previous year) is a reasonable and clinically valid approach to identify a sub-population and one that would allow more severe patients with greater unmet need to be treated with mepolizumab.

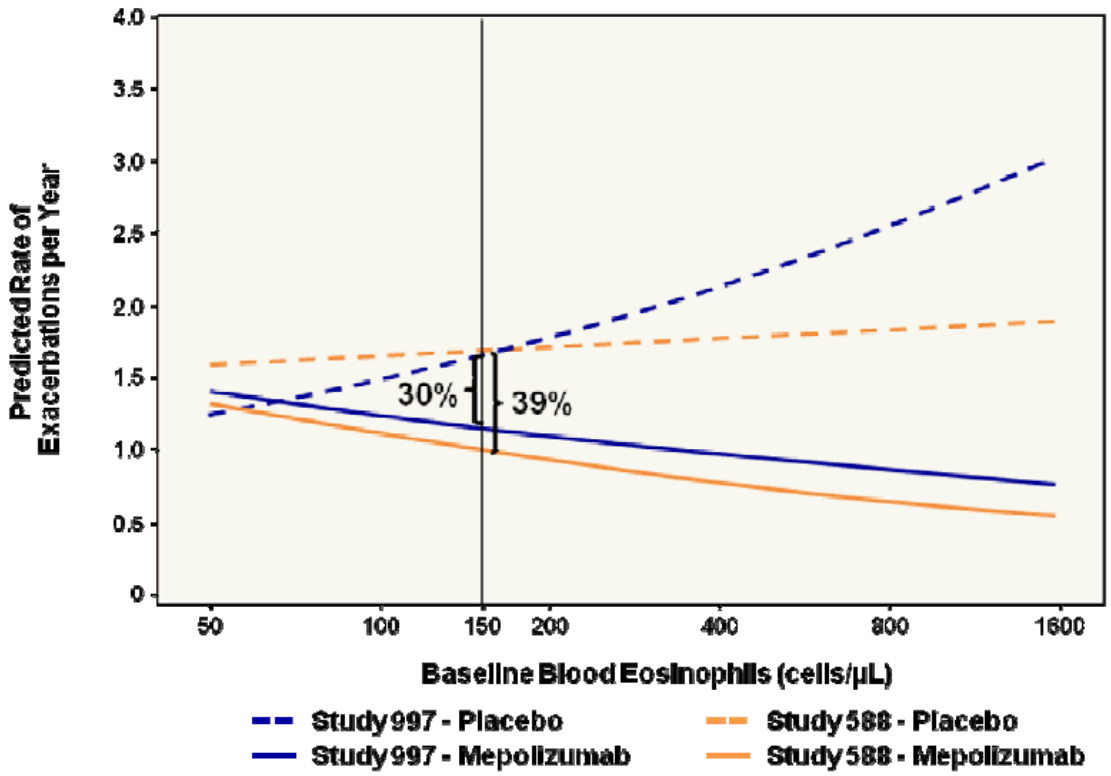
1.4 *Use of Eosinophil Levels to Identify an Appropriate Population for Guidance*

Blood eosinophils are a valid marker of treatment response; mepolizumab is a targeted therapy for patients with eosinophilic inflammation leading to frequent exacerbations or a requirement for daily OCS. Increasing blood eosinophil counts have been shown to be associated with increasing disease severity (ie exacerbation rate) and can also be used to identify patients likely to have clinically meaningful response to mepolizumab treatment.

The ERG and the committee commented that the European Medicines Agency do not currently support a specific eosinophil threshold, highlighting '*eosinophil levels were not sufficiently predictive to justify a specific cut-off within the marketing authorisation*' (ACD section 3.34). We recognise the difficulty in providing an absolute threshold for efficacy, however the eosinophil level does help identify an enhanced responder population amongst the ITT population.

The data suggests that increasing blood eosinophil count in the mepolizumab studies predicts both disease severity and increasing treatment response (Figure 3). In GSK's original submission we presented phase IIb/III trial data (DREAM) for patients selected by 4 diagnostic inclusion criteria predicting eosinophilic airway inflammation (blood eosinophils, sputum eosinophils, exhaled nitric oxide and response to OCS treatment). Blood eosinophils were identified as the most valid marker of treatment response, in addition to baseline exacerbation rate. Blood eosinophil levels of ≥150 cells/µL at screening and ≥300 cells/µL in the last 12 months were the best predictors of response to mepolizumab in SREA patients. A second phase III clinical trial program, MENSA, confirmed their validity of the blood eosinophil thresholds as a predictive treatment biomarker. The evidence therefore supports the proposition that a higher eosinophil level would identify a population with increased disease burden, as evident by more severe inflammatory disease and thus an enhanced capacity to benefit.

Figure 3 Modelling Analysis: Predicted Rate of Exacerbations by Baseline Blood Eosinophil Count (ITT results of DREAM and MENSA)



In order to identify a more restricted group of patients with the greatest potential to benefit and that is cost effective to the NHS, we proposed a selection criterion of ≥150 cells/µL at screening in the company submission for two reasons (please also see company submission section 4.7).

1. In order to restrict the patient population to those with an enhanced capacity to benefit and hence enhanced cost effectiveness.
2. While both ≥150 cells/µL at screening and ≥300 cells/µL in the last 12 months were inclusion criteria in phase III, the ≥150 cells/µL level at screening was chosen as it was a better predictor of enhanced response compared to a historical figure of ≥300 cells/µL in the last

12 months. We acknowledge that this has led to some confusion as 150 cells/µL would be considered within the normal range. We agree that at higher eosinophil level both disease burden and potential for greater absolute benefit increases.

The ability to predict disease severity and treatment response with blood eosinophils is clearly shown in two separate studies in Figure 3. In order to identify patients who are more severe and therefore more likely to get absolute benefit from mepolizumab, and following feedback from clinical experts after publication of the ACD, GSK proposes to further restrict the target population. A higher threshold of ≥300 cells/µL at the time of treatment initiation or in the last 12 months aligns more consistently with the population in which clinical experts said they would seek to use mepolizumab within clinical practice. We provide new evidence of the clinical and cost effectiveness in the >300 cells/µL subgroup for the committee's consideration in section 2.

1.5 *Comparison with omalizumab, and people previously treated with omalizumab*

1.5.1 Comparison with omalizumab

Once dosing restrictions based on the approved market licenses and proposed NICE populations of use are considered of patients eligible for mepolizumab only [redacted] will also be co-eligible for omalizumab.The committee also agreed that there are few patients who clinicians would consider equally likely to receive either drug. For these patients clinicians should have the option to use either medicine rather than being restricted to omalizumab only, which would be the outcome if these recommendations were the basis of guidance (i.e. for those patients where clinicians, based on presenting phenotype, would 'prefer' to use mepolizumab as described in section 4.9 of the ACD they would have no alternative but to use omalizumab.)

We acknowledge there is uncertainty in the NMA that was carried out to inform this comparison. However the primary reason for the uncertainty results from the fact that patient level data for omalizumab is not available to GSK. Given that omalizumab is recommended by NICE in a restricted population and patient level data would be required to undertake a NMA in this specific population, it is inevitable that the NMA would not be feasible in this precise population. Despite this unavoidable limitation, we conducted robust analyses to explore the relative effectiveness. In these analyses the ERG have reported that omalizumab is dominated by mepolizumab (i.e. is more costly and less effective) using the committees 5 core economic assumptions. Given that both medicines would be restricted to a similar and more severe population it is not unreasonable to assume that these results would be supported if a more specific analysis in the restricted populations were feasible.

To not issue guidance on the basis of uncertainty would result in patients being denied access to mepolizumab as an alternative to omalizumab, even though it may be preferred option for the individual patients phenotype and could be cost saving to the NHS. We would therefore ask the committee to reconsider this aspect of the guidance

1.5.2 Guidance for people previously treated with omalizumab

Mepolizumab should be available to patients previously on omalizumab.

The committee states in the ACD in section 4.1, page 32 that '*no data had been presented for using mepolizumab after omalizumab*' and that '*in the absence of data, mepolizumab could not be considered at this stage in the pathway and its guidance for mepolizumab would not apply to people previously treated with omalizumab*'.

As further discussed in section 2, evidence was presented in the company submission which we believe may have not been fully considered in reaching the conclusion to not issue guidance in those patients (see Section 2).

Given that mepolizumab has a different mechanism of action to omalizumab, addresses a different phenotype and data is available in previous omalizumab users showing no difference in effectiveness, we argue that guidance should not be restricted by previous omalizumab use.

1.6 *The most plausible assumptions for consideration listed in the economic model.*

GSK does not believe that the assumptions used by the committee are the most plausible for this appraisal, and suggest that the true cost-effectiveness of mepolizumab has been underestimated in the ACD.

This section addresses the uncertainties that were raised in the economic analyses, from which the draft recommendations were made by the Committee in section 4 of the ACD. We focus on assumptions that have a significant impact on the ICER and which are therefore important to address in order to ensure that the final guidance is sound. In addition we respond to other assumptions raised by the committee:

Key issues addressed:

- Inclusion of exacerbation rate data from COSMOS (and in full in 2.1)
- Direct EQ-5D scores
- Age-related asthma mortality
- Continuation criteria

Additional uncertainties:

- Duration of treatment
- Waning of treatment
- Attrition rate
  Exacerbation rates in those who don't continue treatment
- Age adjusting utilities in the model
- Disutilities based on average duration of exacerbations from MENSA
- Benefit of mepolizumab on symptoms
- Age in the clinical trials and in the UK

We also consider the benefits of mepolizumab not captured in the ICER.

1.6.1 Key issues addressed:

Inclusion of exacerbation rate data from COSMOS (4.14 & 4.15)

The Committee considered that the inclusion of data from COSMOS was preferable to using MENSA. COSMOS was an open label extension study of MENSA and SIRIUS. On completing MENSA or SIRIUS, patients who wished to continue in a study were treated with 100mg SC mepolizumab (237 people from placebo and 414 people from a mepolizumab treatment arm (100mg SC or 75mg IV)). Thus in COSMOS, there was only one mepolizumab treatment arm: there was no placebo arm. The study lasted for one year.

We do agree that COSMOS provides a longer period over which to study the efficacy of mepolizumab; these data were not available to use at the time of the submission. In the absence of

data, the ERG estimated the post continuation criterion (CC) exacerbation rates from COSMOS. These data have now been analysed and are provided in section 2.1, and should be used in any analyses in which COSMOS is applied.

When the ERG adjusted the post continuation criterion exacerbation rates using data from COSMOS they made no adjustments to the SoC arm. However, as the Committee points out, it is important to separate out the underlying rate of exacerbations with standard of care and the relative effect of mepolizumab. GSK believes the appropriate amendment for the SoC arm is to use either the pre-trial enrolment exacerbation rates, or the non responder exacerbation rates in COSMOS (as a proxy for discontinuers), the results of which have been shown to be consistent. Doing this adjustment is more reflective of real-world exacerbation rates in these patients, and ensures like for like data are used in the analyses.

This adjustment has been conducted in section 2. To summarise the results from this analysis, it is shown that separating out this underlying effect results in lower ICER estimates because doing so means that the difference in exacerbation rates in the mepolizumab and SoC arms of the model widens.

We therefore believe that if COSMOS is used to inform the post continuation criterion exacerbation rates, then the SoC arm should also be adjusted to reflect 'real world' rates.

Utilising direct EQ-5D scores in the model (4.17)

The ACD concludes that direct EQ-5D values would be preferable to include within the model.

However, there are a number of limitations to utilising EQ-5D values from the phase IIb/III DREAM trial, and these are described below. There is good reason to believe that the issues with the EQ-5D in this population lead to an overly conservative estimate of the health related quality of life (HRQoL) benefit of mepolizumab, and thus an inflated ICER at the higher range of plausibility.

1. Size of population and treatment arm

The EQ-5D data in DREAM comes from a relatively small population (n=127).MENSA on the other hand has almost three times the number of patients from whom HRQoL can be obtained; 175 from the 75mg IV arm and 185 from the 100mg SC arm of the trial (n=360), thus more confidence in the results can be achieved. Further in MENSA, HRQoL was collected in the licensed formulation (100mg SC arm), whereas in DREAM this formulation was not present in the trial.

2. Ceiling effect of EQ-5D in DREAM

Patients in the mepolizumab clinical program had severe disease. They experienced frequent exacerbations despite high dose ICS, additional controllers, and in many patients, OCS therapy. In DREAM however, one third of patients reported perfect health on the EQ-5D at baseline despite their disease severity, suggesting that there are ceiling effects in this population. In these patients, using the EQ-5D directly means that it is not possible to capture any improvement in HRQoL in one third of the trial population.

Given the 5 domains in the EQ-5D (mobility, self care, usual activities, discomfort/pain and mental health) people in this population may have adapted to their ill health and restrictions on these domains, particularly 'usual activities' may have become normalised. Clinical experts who we have discussed these results with have also questioned the representativeness of the EQ-5D results in this population.

3. Using SGRQ mapped to EQ-5D alleviates ceiling effects

The ACD suggests that by using the mapping algorithm any limitations of the EQ-5D would still apply. However, by using SGRQ to map to EQ-5D, the issue of the ceiling effect from the EQ-5D is addressed to some degree. This is because patients reporting 'perfect health' in EQ-5D can have less than perfect health as measured and picked up by the SGRQ. Because of this, there is also more capacity to see change in HRQoL over time, because in the EQ-5D, a subject may answer as being in perfect health at multiple observations, whereas the SGRQ is a more sensitive instrument, and is thus more likely to pick up different HRQoL values between multiple observations (compared to the 5 general items of EQ-5D, SGRQ includes 50 respiratory specific items with 72 weighted responses).

To conclude, whilst the EQ-5D utility was explored in sensitivity analysis, GSK believes using the SGRQ-derived utility in the base case is more likely to capture HRQoL benefits in people with severe asthma. If the direct EQ-5D scores are preferred by the committee, we believe that it is important to acknowledge that this is likely to underestimate the HRQoL benefit and therefore cost effectiveness of mepolizumab compared with SoC.

Age related asthma mortality in the model (4.19)

The Committee concluded that the ERG's approach to estimating asthma related mortality was appropriate. Recent discussions with asthma clinical specialists in response to the ACD have highlighted that age adjusting asthma mortality following a hospitalisation is not supported by clinical experience. This age adjustment is the primary justification the ERG gives for wishing to age adjust Watson based on Roberts.

Roberts and Watson report on different outcomes, which cannot be assumed to have the same characteristics.

- In Roberts et al, the authors reported the risk of mortality from any cause following an asthma hospitalisation (looking at a large population cohort of asthmatics with a range of severities in the study), during the hospital visit and at home and, this is what they showed increased with age.(4)

- In Watson, the authors reported on the risk of mortality from asthma during the admission spell itself, for people hospitalised for acute severe asthma (focussed on ICD-10 codes of J46 – severe asthma and J45 – asthma). After the age of 45years, the authors reported a constant risk .(5)

In the model, the background mortality rate (i.e. mortality from any cause) is factored in as per standard methodology, and has been modelled to increase with age. Mortality from asthma however, is a specific element of the model, so it is appropriate that we captured it from the most relevant source, i.e. Watson.

Note that using the assumption on mortality which was applied to calculate the most plausible ICER in TA278, (7) (using the midpoint mortality estimates between Watson et al and de Vries et al. (75), increased by 15% to account for very severe disease), reduces the ICER below that calculated by NRAD plus Watson, from £31,659 to £21,035 per QALY gained in the ITT population. We consider that Watson provides the best source of data for asthma related mortality following a hospitalisation, in this severe asthma population, and that it would be in itself a conservative assumption, in comparison with NICE precedence from TA278.

The continuation criteria (4.13)

1. Validity of the continuation criterion

A continuation criterion (CC) was proposed by GSK whereby only patients whose annualised exacerbation rate improved or remained the same were assumed to continue on treatment. New analyses presented in section 2, show how applying the continuation criterion to MENSA and within COSMOS clearly separates out apparent responders from non responders. For example, of those in MENSA in the ITT population, who met the CC and went into COSMOS, the exacerbation rate per year was 0.74, whereas those who did not meet the CC, on treatment, had a rate of 3.70. It therefore is clear that applying the continuation criterion in the model, in line with the SmPC, is valid. See section 2 for further details.

2. The wording of the continuation criterion

The Committee raised concerns that it may be more appropriate that only those patients whose exacerbation rate improves remain on treatment, and those patients whose exacerbation rate remained stable or worsened discontinue mepolizumab. GSK conducted additional analyses which demonstrated that the majority of patients in MENSA met the criteria (Table 2) and indeed there were no patients that demonstrated no change in exacerbation rate. Our assumptions used for the modelling were intended as a proxy to this clinical review, and altering the assumptions to address this concern would not change the ICER.

Table 2 Proportion of patients experiencing no change or an improvement in exacerbation rate compared to baseline, in MENSA (%)

Compared to baseline:	**Placebo (N=64)**	**Mepolizumab 75mg IV (N=65)**	**Mepolizumab 100mg SC (N=78)**
N who experienced an improvement or no change	52	62	70
Proportion of patients with an improvement in exacerbation rate	0.81	0.95	0.90
Proportion of patients with no change in exacerbation rate	0.00	0.00	0.00

However we believe it remains important to allow patients the option of continuing treatment at clinical discretion despite not demonstrating improved exacerbation rate, as patients may be experiencing benefits in symptoms or HRQoL benefits, or a reduction in OCS exposure.

1.6.2 Additional uncertainties:

1. Duration of treatment

As mentioned in the ACD, there is uncertainty around how long people would be on treatment with mepolizumab. In the model, a base-case assumption of 10 years on treatment was used. This was supported by clinicians at an advisory board, as well as being identical to the duration of treatment used in TA278 for omalizumab. However sensitivity analyses previously presented to the Committee through our submission show that the ICER is stable in response to changes in the duration of treatment, up to and including lifetime: in the ITT population, the ICER for treatment duration of 5 years =£31,966, 10 years = £31,659, lifetime = £32,130. So whilst recognising there is some

uncertainty in this parameter, the committee can be reassured that the impact of this on the ICER would be minimal.

2. Waning of treatment

The assumption of continued efficacy was discussed by the Committee and it was suggested that a scenario exploring a waning effect of mepolizumab would be valuable. The assumption of continued efficacy of mepolizumab over time is supported by data from the COSMOS study (6). This has shown that patients continue to benefit in terms of asthma control (exacerbation rate) and mOCS reduction without a waning effect when continued on add-on mepolizumab treatment.

Furthermore, there is no clinical reason to expect that the efficacy of mepolizumab would wane over time. While antibodies were observed in a small number of patients (see company submission), none of the patients found to have antibodies experienced a loss of efficacy to mepolizumab. Also, antibodies typically developed during the first 4 months of treatment and were mostly transient in nature. The available data support this assumption. Nevertheless, GSK is continuing to collect evidence on the effectiveness of treatment over time. The assumption of continued effectiveness was discussed at the Committee meeting and was supported by the clinical experts present. There is currently no functionality within the economic model to provide an analysis where the impact of mepolizumab on exacerbations is reduced over time. However, in the response to question 2, we have provided additional analyses which explore the sensitivity of the results to using a higher exacerbation rate after year 1, as per the data obtained from COSMOS, which would increase the ICER (see section 2.1).

3. The attrition rate (4.13)

In the model, a 10% year on year attrition rate post year 1 was assumed because in COSMOS (the one year extension study of MENSA and SIRIUS), 90% of people who entered, remained in the study after one year. To provide reassurance on the stability of the ICER when changing the attrition rate, a sensitivity analysis was run, with attrition rates of 2%, 5%, 10%, and then higher attrition rates of 20% and 50%. These all gave ICERs around £32,000 per QALY gained in the GSK ITT population (Table 3.). Therefore, given that the ICER's remain relatively stable we do not believe this is a source of uncertainty in the cost effectiveness estimates**.**

Table 3 Impact of lifetime treatment duration and a range of attrition rates on the ICER (MENSA ITT)

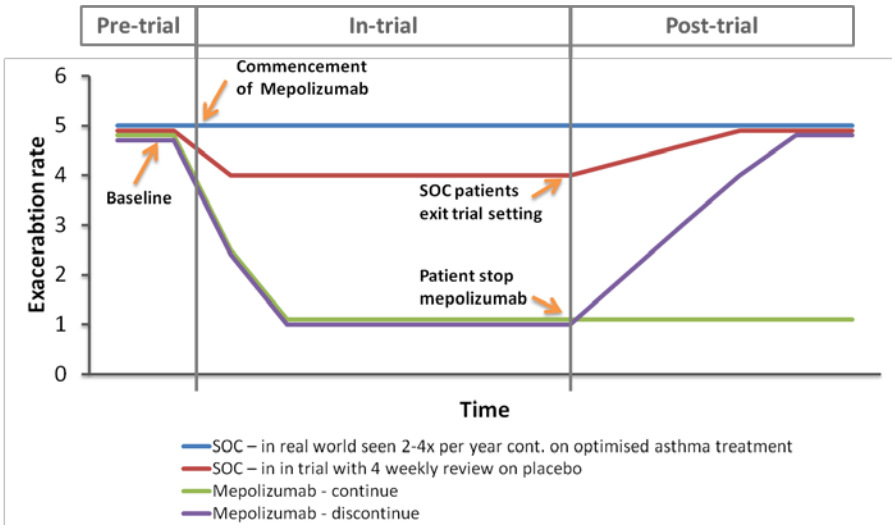
Attrition rate	**ICER**
2%	£31,578
5%	£31,611
10%	£31,670
20%	£31,807
50%	£32,465

4. Exacerbation rates in those who don't continue treatment (4.14)

The ACD highlights that once patients discontinue mepolizumab in the model, it was assumed that their exacerbation rate is the same as those patients in the SoC group, who had never had mepolizumab. The Committee was concerned that that this may over estimate the benefit of mepolizumab. However in real life (as we see pre-trial), the exacerbation rates of patients on SoC are much higher than in-trial, due to the placebo effect. Therefore, patients who discontinue treatment with mepolizumab would return to a higher exacerbation rate than in-trial, which would result in a decrease, rather than increase the ICER (as the ACD suggests) because the difference in the relative rates widens (see Figure 4).

This is supported by published evidence from a 12 months follow up study in patients who were on mepolizumab for 12 months which showed that after discontinuation from mepolizumab, both blood eosinophil levels and the asthma exacerbation rate returned to pre-trial levels (i.e. discontinuation of mepolizumab results in patients returning to their baseline disease state (7)).

Figure 4 SREA patients' expected exacerbation rates based on clinical and trial evidence



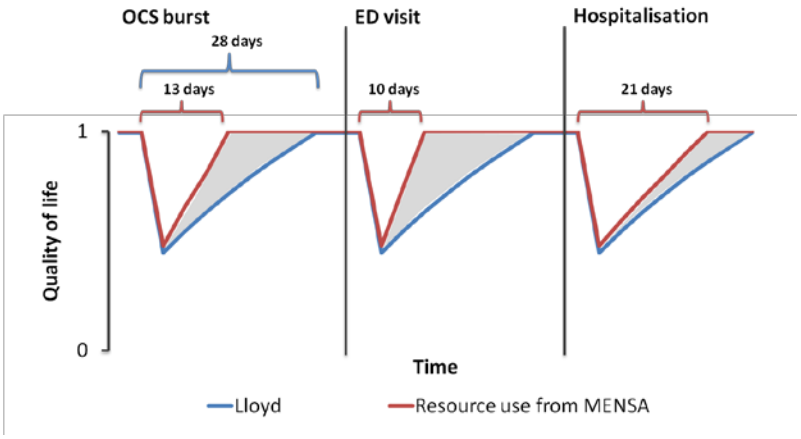
5. Age adjusting utilities in the model (4.18)

The Committee suggested that utilities should be age adjusted. However, because the starting age is the same in both arms of the analysis (the mean age of the model in the base case is 50.1 years), any increment/decrement applied to the health states would be adjusted in all arms by the same amount, and so they would likely cancel out. To apply an age adjusted value for the disutility from an exacerbation would require data on which direction, and which value to age adjust to. In the absence of any data on this, we believe the method applied is appropriate, and thus results based on this assumption would be appropriate.

6. Disutilities based on average duration of exacerbations from MENSA (4.18)

The ERG suggested incorporating the average length of exacerbation type based on data from MENSA rather than the 28 days applied to all exacerbation types in the GSK base case from Lloyd et al. However the duration of an exacerbation from the MENSA trial was calculated based on the time during which a patient was actively receiving OCS treatment and could underestimate the time during which patients' HRQoL would be affected by an exacerbation. There would be a tail end of the exacerbation once resource use has finished, when the utility decrement continued for longer, giving a censored duration of an exacerbation (see Figure 5).

Figure 5 Visual representation of using MENSA resource use rather than Lloyd to capture utilities in the model



To apply the exacerbation duration from MENSA rather than Lloyd to the model would be to go against precedent previously set by NICE. In TA278 (omalizumab) the Assessment Group proposed that the duration of weeks used in the model should be 4 weeks as per Lloyd, rather than the duration of an exacerbation as seen in the trial, INNOVATE. This formed the basis of the key model assumptions used by the Assessment Group and was accepted by the committee as a basis for guidance.

7. Benefit of mepolizumab on symptoms

The ACD states that the Committee heard from the clinical experts that mepolizumab was unlikely to have an effect on symptoms. This was surprising because the clinical data that was submitted clearly show that patients experience a significant improvement in their quality of life and asthma control and thus an improvement in symptoms. In MENSA in the GSK PP, the SGRQ improved from 6.4 to 12.8 units (MCID = 4 units), and there was a statistically significant improvement in asthma control (ACQ-5), from 0.42 to 0.96 units (MCID 0.5). Further, the values for the individual health states in the model were derived from an analysis of the HRQoL of the different groups within MENSA. We therefore believe that it is appropriate to have different utility values for mepolizumab compared with the standard of care health state and therefore this would not result in an over-estimation in the model.

8. Age in the clinical trials and in the UK (4.20)

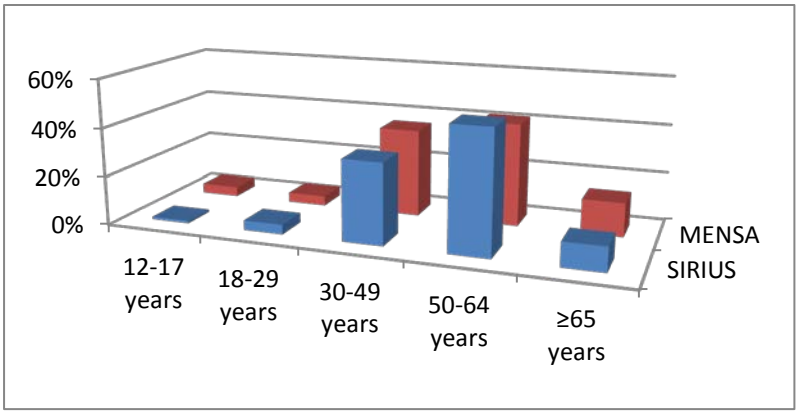
The ACD highlights that the Committee expresses interest in seeing registry or observational data on the age distribution of patients in the UK, in order to validate the model. Data from two UK based studies, one a cross-sectional registry of 382 refractory asthma patients (8) and a second, a historical cohort study of 20,929 primary care patients with eosinophilic inflammation (9) found that the average age at presentation was 44.9 (SD 13.7) and 45.0 (range 31-61) years, respectively, whereas the British Thoracic Society showed that UK patients in the BTS Difficult Asthma Registry had an average age of 50 years (1).

The starting age of the cohort in the model was 50.1 years as it was the mean age of patients recruited into MENSA. Figure 6. presents the age distribution of patients in MENSA and in SIRIUS. Further, results from a recently reported, cross-sectional study(IDEAL) (10) describing characteristics of patients with severe asthma found that the average age for all patients was 50.5 (SD 15.6) years and those deemed eligible for mepolizumab was 48.0 (SD 15.5) years.

Given the age ranges in the registry, observational and trial data above, we consider that a starting age of 50.1 years in the model is consistent with the average age seen in clinical practice for these

severe asthmatics in England and Wales. Therefore we do not believe this should be considered this a major source of uncertainty.

Figure 6 Age distribution of patients in MENSA and SIRIUS



1.6.3 Benefits of mepolizumab not captured in the ICER (4.23)

The committee agreed that some benefits related to avoiding maintenance OCS use had not been fully captured in the QALY measure and that benefits to carers may not have been captured in the QALY. The long-term health benefits of reducing OCS exposure were difficult to capture fully in the economic evaluation, nevertheless, the evidence suggests that accounting for this treatment benefit would be likely to reduce the ICER to below the base case ICER.

Benefits to carers were not included in the model, and this was highlighted in the committee meeting. Initial investigations suggest that accounting for this additional treatment benefit would also be likely to reduce the ICER to below the base case ICER. It was not possible to obtain an estimate of the size and scale of this benefit in the timeframe of the ACD response.

Finally given the ceiling effects demonstrated in EQ-5D measurements within DREAM (30% of all patients reported perfect health at baseline despite severe disease) the ICER when applying the direct EQ-5D values is not likely to fully capture the quality of life benefits in these patients.

Therefore when considering the most plausible ICER it is important to note that there are a number of factors that may not be fully quantified and therefore the benefits of mepolizumab would not be fully captured in the ICER.

2 Has all the relevant evidence been taken into account?

Based on feedback and the content of the ACD, three additional analyses are presented below, to ensure that all the relevant evidence is able to be taken into account by the Committee:

Analysis 1:

The Committee's preferred population as per the ACD in terms of cost effectiveness is a population not limited by blood eosinophil count, with ≥2 exacerbations in the previous year and limited to refractory patients having maintenance OCS (i.e. continuous OCS). The ACD states that evidence for this population was not available to the committee and therefore we provide this analysis for consideration at the second meeting.

Mindful of both the unmet clinical need in severe asthma and the resource constraints of NHS England there remains a need to identify a clinically plausible subgroup with an enhanced capacity to benefit from mepolizumab. However, as this is the first specific treatment for eosinophilic asthma, it is recognised that there is uncertainty as to how to define the preferred population. Therefore, 2 additional analyses are submitted to inform the committee's discussions (Analysis 2 and 3).

Analysis 2:

This analysis presents the clinical and cost effectiveness results for a population with ≥4 exacerbations in the previous year or dependence on maintenance OCS. Further, given that an exacerbation would require at least a course of OCS, we believe that this is consistent with the existing omalizumab guidance, which states that patients must have a '*need for continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)*'.

Analysis 3:

Following publication of the ACD, clinical experts have fed back that they do believe there is a role for blood eosinophil levels in identifying a responder population, especially as mepolizumab is a biomarker-driven treatment (see section 1.4). However they would see this at a higher level than was proposed initially (≥150 cells/µL). This is consistent with the views of the ERG clinical advisors and the experts present on the day of the ACM. Therefore analysis 3 includes the higher blood eosinophil level of ≥300 cells/µl in the last year with a need for continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year).

In addition:

- Data and additional analyses are provided based on outputs from the COSMOS trial to inform post-continuation criterion exacerbation rates.
- Additional clinical data are presented for mepolizumab, showing the efficacy in patients previously treated with omalizumab. This is in addition to data provided in the company submission.
- With a number of points within the ACD (both in the comparison with SOC and omalizumab it states that the most appropriate evidence to inform the appraisal is from SIRIUS as this reflects patients requiring maintenance OCS. As discussed previously we believe the population should be extended to include patients requiring frequent courses of oral corticosteroids. For this population the most appropriate evidence to inform the analysis would be that from MENSA supported by DREAM (which includes patients on continuous and frequent courses of OCS). SIRIUS would only be the most appropriate evidence when considering the potential to reduce dependency on oral corticosteroids. Therefore we believe the evidence from MENSA has not been fully taken into account.

2.1 *Incorporating COSMOS data to set exacerbation rates for those meeting the continuation criteria*

In section 4.15 of the ACD it questions the use of data from MENSA as the most appropriate estimate of effectiveness after the application of a continuation rule at 12 months and mentions that *'the inclusion of data from COSMOS was preferable'* and that it is *'important to separate the underlying rate of exacerbations with standard of care and the relative effect of mepolizumab'*. See section 1.6.1.

The ACD states a preference for the exacerbation rates for mepolizumab from the open-label extension study COSMOS over the MENSA rates, following the application of the continuation criteria (CC), as it may be more reflective of real world efficacy. However, the ERG group made no adjustment to the exacerbation rates for the SOC arm, leaving them as the MENSA in-trial values. This is an inappropriate comparison and this failure to adjust the SOC rates was acknowledged as a short-coming in the ACD. If there is a preference for the use of COSMOS exacerbation rates for mepolizumab, then the SOC rates should also be amended.

As COSMOS is a single-arm extension study of MENSA and SIRIUS there is no possibility of gathering exacerbation rates for SoC. Therefore the closest real world values for SoC exacerbation rates are the pre-enrollment rates from MENSA as these will be an accurate reflection of real-world outcomes.

An alternative approach would be to use exacerbation rates for patients who did not meet the continuation criteria. Whilst these patients continued with mepolizumab therapy within COSMOS, albeit as non-responders, the estimates from these patients could be considered as a proxy for SoC.

It can be seen from the data that the exacerbation rates for SoC and for these non responders are consistent and that they show a clear and sizeable benefit of treatment with mepolizumab in those who respond. In the group with continuous or frequent use of OCS (analysis 2), the exacerbation rate post CC in COSMOS was 1.02. This compares with a rate of 5.26 per year in those who are still receiving treatment in COSMOS, but were non-responders, and a rate of 5.10 in the pre-trial SoC arm in MENSA (Table 4).

Table 4 Annual exacerbation rates for patient used in the model health states (bold), with corresponding exacerbation rates from alternative sources

	ITT	≥4 exac or mocs	≥300 eos ≥4 exac or mocs
Pre continuation (yr 1) health state for mepolizumab			
In MENSA	**0.88**	**1.36**	**1.34**
Post CC health state for mepolizumab			
In MENSA	**0.55**	**0.77**	**0.73**
In COSMOS from MENSA	0.74	1.02	1.02
Post CC discontinuation health state for SOC			
SOC			
SOC pre-trial	3.6	5.10	5.20

MENSA			
SOC in-trial MENSA	**1.74**	**2.74**	**2.58**
Not meeting CC as a potential proxy for discontinuation (still on treatment)			
MENSA	2.51	2.77	2.77
COSMOS from MENSA	3.70	5.26	5.26

2.2 *Analysis 1: ITT restricted to maintenance OCS patients*

Whilst we feel it is not appropriate to restrict guidance to maintenance OCS users only, an adaptation of the economic model was conducted and additional analyses were undertaken to explore the scenario restricting to maintenance OCS patients only, using our base case assumptions from the original submission. The data inputs into the model for all three analyses are presented in Appendix 2.

The results are shown in Table 5. Restricting the population to the maintenance OCS group, increases the ICER slightly to £31,734; the ICER in the whole ITT population is £31,659. As would be expected, the absolute QALYs are lower when restricted to maintenance OCS compared with excluding mOCS, but the difference in costs and QALYs between the groups is similar.

Note that none of these ITT populations are likely to be cost effective when applying the Committee's base case assumptions to the modeling.

However if alternative estimates of exacerbation rates post-continuation criterion are utilized together with revised SoC exacerbation rates the ICERs would be significantly improved and would be cost effective.

Table 5 Model results, ITT population, with different maintenance OCS scenarios, with PAS

	Total cost	**∆ Costs**	**Total QALYs**	**∆ QALYs**	**ICER (vs.)**
ITT restricted to people on mOCS					
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£31,734
Full ITT (+- mOCS)					
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£31,659

2.3 *Analysis 2: need for continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)*

For the reasons above and in section 1, data is provided on the clinical (Table 6, Table 7 and Table 8) and cost-effectiveness in an SREA population in whom there is the need for continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year).

Table 6 Efficacy results for subgroup of patients with a need continuous or frequent treatment with oral corticosteroids for DREAM, MENSA and SIRIUS

		ITT vs. subgroup (≥4 exacerbations or mOCS users)																	
		ITT				DREAM				ITT			MENSA			ITT		SIRIUS	
		Pbo	75mg IV	250mg IV	750mg IV	Pbo	75mg IV	250mg IV	750mg IV	Pbo	100mg SC	75mg IV	Pbo	100mg SC	75mg IV	Pbo	100mg SC	Pbo	100mg SC
Rate of Clinically Significant Exacerbations	n	155	153	152	156	66	70	72	70	191	194	191	77	102	88	66	69	66	69
	Exacerbation rate/year	2.4	1.24	1.46	1.15	3.12	1.33	1.41	1.30	1.74	0.83	0.93	2.74	1.48	1.22	2.12	1.44	2.12	1.44
Comparison vs placebo	Rate ratio		**0.52**	**0.61**	**0.48**		**0.43**	**0.45**	**0.42**		**0.47**	**0.53**		**0.54**	**0.44**		**0.68**		**0.68**
	95% CI		0.39, 0.69	0.46, 0.81	0.36, 0.64		0.29, 0.63	0.31, 0.65	0.28, 0.61		0.35, 0.64	0.40, 0.72		0.37, 0.79	0.29, 0.67		0.47, 0.99		0.47, 0.99
	p value		<0.001	<0.001	<0.001		<0.001	<0.001	<0.001		<0.001	<0.001		0.002	<0.001		0.042		0.042
Rate of Exacerbations requiring Hospitalisation or ED visits	n	155	153	152	156	66	70	72	70	191	194	191	77	102	88	66	69	66	69
	Exacerbation rate/year	0.43	0.17	0.25	0.22	0.63	0.21	0.29	0.18	0.2	0.08	0.14	0.54	0.24	0.12	0.22	0.08	0.22	0.08
Comparison vs placebo	Rate ratio		**0.4**	**0.58**	**0.52**		**0.33**	**0.47**	**0.29**		**0.39**	**0.68**		**0.44**	**0.23**		**0.35**		0.35
	95% CI		0.19, 0.81	0.30, 1.12	0.27, 1.02		0.14, 0.78	0.22, 1.02	0.12, 0.69		0.18, 0.83	0.33, 1.41		0.19, 1.00	0.09, 0.62		0.09, 1.40		0.09, 1.40
	p value		0.011	0.106	0.056		0.012	0.055	0.005		0.015	0.299		0.049	0.003		0.136		0.136
Rate of Exacerbations requiring Hospitalisation	n	155	153	152	156	66	70	72	70	191	194	191	77	102	88	**Due to insufficient events no analysis of hospitalisation rate could be performed**			
	Exacerbation rate/year	0.18	0.11	0.12	0.07	0.32	0.14	0.19	0.07	0.1	0.03	0.06	0.33	0.09	0.05				
Comparison vs placebo	Rate ratio		**0.61**	**0.65**	**0.37**		**0.42**	**0.58**	**0.22**		**0.31**	**0.61**		**0.28**	**0.14**				
	95% CI		0.28, 1.33	0.31, 1.39	0.16, 0.88		0.16, 1.11	0.25, 1.37	0.07, 0.66		0.11, 0.91	0.23, 1.66		0.08, 0.99	0.03, 0.66				
	p value		0.214	0.268	0.025		0.08	0.215	0.007		0.034	0.334		0.049	0.012				
SGRQ	n	**SGRQ was not an endpoint in DREAM**								177	184	174	72	97	79	61	65	61	65
	LS Mean (SE)									37.7 (1.16)	30.7 (1.13)	31.2 (1.16)	41.5 (1.93)	34 (1.67)	34.6 (1.86)	44.3 (1.73)	38.5 (1.68)	44.3 (1.73)	38.5 (1.68)
	LS Mean Change (SE)									-9.0 (1.16)	-16.0 (1.13)	-15.4 (1.16)	-9.3 (1.93)	-16.8 (1.67)	-16.2 (1.86)	-3.1 (1.73)	-8.8 (1.68)	-3.1 (1.73)	-8.8 (1.68)
Comparison vs placebo	Difference										**-7**	**-6.4**		**-7.5**	**-6.9**		**-5.8**		**-5.8**
	95% CI										-10.2, -3.8	-9.7, -3.2		-12.5, -2.5	-12.2, -1.6		-10.6, -1.0		-10.6, -1.0
	p value										<0.001	<0.001		0.004	0.11		0.019		0.019
ACQ[1]	n	121	127	126	129	48	56	57	54	170	173	161	70	94	75	53	58	53	58
	LS Mean (SE)	1.72 (0.087)	1.56 (0.087)	1.45 (0.086)	1.52 (0.086)	1.96 (0.16)	1.81 (0.154)	1.49 (0.151)	1.65 (0.153)	1.7 (0.069)	1.26 (0.068	1.28 (0.070)	1.96 (0.107)	1.36 (0.093	1.46 (0.103)	1.98 (0.128)	1.46 (0.126)	1.98 (0.128)	1.46 (0.126)
	LS Mean Change (SE)	-0.59 (0.087)	-0.75 (0.087)	-0.87 (0.086)	-0.80 (0.086)	-0.53 (0.16)	-0.68 (0.154)	-1.0 (0.151)	-0.84 (0.153)	-0.50 (0.069)	-0.94 (0.068)	-0.92 (0.070)	-0.41 (0.107)	-1.01 (0.093)	-0.9 (0.103)	-0.09 (0.128)	-0.61 (0.126)	-0.09 (0.128)	-0.61 (0.126)
Comparison vs placebo	Difference		**-0.16**	**-0.27**	**-0.2**		**-0.15**	**-0.47**	**-0.31**		**-0.44**	**-0.42**		**-0.6**	**-0.49**		**-0.52**		**-0.52**
	95% CI		-0.39, 0.07	-0.51, -0.04	-0.43, 0.03		-0.57, 0.27	-0.89, -0.06	-0.73, 0.11		-0.63, -0.25	'-0.61, -0.23		-0.88, -0.32	-0.79, -0.20		-0.87, -0.17		-0.87, -0.17
	p value		0.183	0.02	0.085		0.48	0.026	0.149		<0.001	<0.001		<0.001	0.001		0.004		0.004

Table 7 Meta-analysis efficacy results for subgroup of patients with a need continuous or frequent treatment with oral corticosteroids for DREAM, MENSA and SIRIUS

		ITT population[2]			Subgroup (≥4 exacerbations or mOCS users)					
		Meta-analysis of DREAM and MENSA			Meta-analysis of DREAM and MENSA			Meta-analysis of DREAM, MENSA plus SIRIUS		
		Pbo	75mg IV / 100mg SC	All Doses	Pbo	75mg IV / 100mg SC	All Doses	Pbo	75mg IV / 100mg SC	All Doses
Rate of Clinically Significant Exacerbations	n	346	538	846	143	260	402	209	329	471
	Rate ratio		0.51	0.53		**0.47**	**0.46**		**0.52**	**0.51**
	95% CI		0.42, 0.62	0.44, 0.62		0.36, 0.60	0.37, 0.57		0.43, 0.65	0.42, 0.62
Comparison vs placebo	p value		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001
Rate of Exacerbations requiring Hospitalisation or ED visits	n	346	538	846	143	260	402	209	329	471
	Rate ratio		**0.53**	**0.60**		**0.33**	**0.35**		**0.34**	**0.35**
	95% CI		0.33, 0.84	0.40, 0.89		0.19, 0.59	0.22, 0.58		0.20, 0.57	0.22, 0.56
Comparison vs placebo	p value		0.007	0.012		<0.001	<0.001		<0.001	<0.001
Rate of Exacerbations requiring Hospitalisation	n	346	538	846	143	260	402	**Due to insufficient events in SIRIUS no analysis could be performed**		
	Rate ratio		0.50	0.49		**0.32**	**0.34**			
	95% CI		0.28, 0.89	0.30, 0.81		0.15, 0.68	0.18, 0.64			
Comparison vs placebo	p value		0.018	0.005		0.003	<0.001			
SGRQ[3]	n	**No analysis possible as no SGRQ results in DREAM**			**No analysis possible as no SGRQ results in DREAM**			133	162	241
	Difference								**-6.6**	**-6.5**
Comparison vs placebo	95% CI								-10, -3.2	-9.8, -3.3
	p value								<0.001	<0.001
ACQ[4]	n	298	465	732	141	250	389	207	318	457
	Difference		**-0.34**	**-0.29**		**-0.45**	**-0.47**		**-0.47**	**-0.48**
Comparison vs placebo	95% CI		-0.48, -0.20	-0.42, -0.17		-0.66, 0.22	-0.67, -0.27		-0.65, -0.29	-0.66, -0.31
	p value		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001

Table 8 OCS reduction results for subgroup of patients with a need continuous or frequent treatment with oral corticosteroids for SIRIUS

		SIRIUS			
		ITT		≥4 exacerbations or mOCS users	
		Pbo	100mg SC	Pbo	100mg SC
% OCS reduction during week 20-24	90% - 100% **(%)**	7(11)	16 (23)	7(11)	16 (23)
	75% - <90% **(%)**	5 (8)	12 (17)	5 (8)	12 (17)
	50% - <75% **(%)**	10 (15)	9 (13)	10 (15)	9 (13)
	>0% - <50% **(%)**	7 (11)	7 (10)	7 (11)	7 (10)
	No change or any increase or lack of asthma control or withdrawal from treatment (%)	37 (56)	25 (36)	37 (56)	25 (36)
Comparison vs placebo	Odds Ratio to Placebo		2.39		2.39
	95% CI		1.25, 4.56		1.25, 4.56
	p-value		0.008		0.008

		SIRIUS			
		ITT		≥4 exacerbations or mOCS users	
		Pbo	100mg SC	Pbo	100mg SC
≥50% Reduction in Daily OCS Dose, n (%)	n	66	69	66	69
	50% to 100%	22 (33)	37 (54)	22 (33)	37 (54)
	<50%, no decrease in OCS, lack of asthma control, or withdrawal from treatment	44 (67)	32 (46)	44 (67)	32 (46)
Comparison vs placebo	Odds ratio to placebo		**2.26**		**2.26**
	95% CI		1.10, 4.65		1.10, 4.65
	p-value		0.027		0.027
Reduction in Daily OCS Dose to ≤5 mg, n (%)	n	66	69	66	69
	Reduction to ≤5 mg	21 (32)	37 (54)	21 (32)	37 (54)
	Reduction to >5 mg, lack of asthma control, or withdrawal from treatment	45 (68)	32 (46)	45 (68)	32 (46)
Comparison vs placebo	Odds ratio to placebo		**2.45**		**2.45**
	95% CI		1.12, 5.37		1.12, 5.37
	p-value		0.025		0.025
Total Reduction of OCS Dose, n (%)	n	66	69	66	69
	Total (100%) reduction (0 mg)	5 (8)	10 (14)	5 (8)	10 (14)
	OCS taken, lack of asthma control, or withdrawal from treatment	61 (92)	59 (86)	61 (92)	59 (86)
Comparison vs placebo	Odds ratio to placebo		**1.67**		**1.67**
	95% CI		0.49, 5.75		0.49, 5.75
	p-value		0.414		0.414
Median Percentage Reduction in Daily OCS Dose	n	66	69	66	69
	Median (%)	0.0	50.0	0.0	50.0
	95% CI of the median	-20.0, 33.3	20.0, 75.0	-20.0, 33.3	20.0, 75.0
	Median difference		**-30.0**		**-30.0**
Comparison vs placebo	95% CI of the median difference		-66.7, 0.0		-66.7, 0.0
	p-value		0.007		0.007

When looking at the rate of clinically significant exacerbations in the individual exacerbation studies (DREAM, MENSA) in Table 6 above, the relative reduction in exacerbations between the ITT and subgroup is similar (47% to 58%). This is further reinforced by the meta-analysis data of DREAM and MENSA combined and including a sensitivity analysis of SIRIUS (47% to 54%) shown in Table 7. As discussed in section 1, although the relative improvement remains the same, the clinical benefit is seen in the absolute (numerical) reduction in exacerbations between the two populations. Demographics for this sub-group can be found in appendix 1.

When comparing ACQ scores, it can be seen in the meta-analysis data that there is a greater, statistically significant improvement in the subgroup compared to the ITT population. In the MENSA 100mg SC arm, the subgroup achieved a statistically and clinically significant improvement in ACQ score of 0.6 compared to placebo.

An adaptation of the economic model was conducted and additional analyses were undertaken to explore this scenario. Data inputs into the model are listed in Appendix 2. For ease of comparison, the base case results using the assumptions that went into our original company submission were used. A series of sensitivity analyses that reflect the discussions in the Committee were then undertaken to assess how the ICER varies when different selected assumptions are applied to the model (see Table 9) including:

1. Direct EQ-5D scores
2. Lifetime treatment duration
3. Disutilities based on duration of exacerbation in MENSA
4. CC exacerbation rate from COSMOS

These reflect the assumptions set out in 4.21 of the ACD as being those presented by the ERG, with the exception of one adjustment: age-related asthma mortality where we consider that our original approach is more appropriate (see section 1.6).

Two additional scenarios are also explored and presented in Table 9:

5. CC exacerbation rate from COSMOS and SOC exacerbation rate in 12 months prior to entering MENSA
6. CC exacerbation rate and SOC set to non-responders from COSMOS

Table 9 Results of analysis 2: need for continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year), base case and scenario analyses (with PAS)

Sensitivity analysis		GSK sub-population				
		Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)
N/A	**Base-case**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£22,305
1	**Direct EQ-5D scores**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£27,916
2	**Lifetime treatment duration**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£22,569
3	**Duration of an exacerbation from MENSA rather than Lloyd**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£22,888

4	**CC exacerbation rate from COSMOS (1.02), SOC MENSA in-trial (2.74)**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]		[redacted]		£24,105
5	**CC exacerbation rate from COSMOS (1.02), SOC MENSA pre-trial (5.10)**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]		[redacted]		£14,788
6	**CC exacerbation rate (1.02), SOC set to non-responders from COSMOS (5.26)**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]		[redacted]		£14,484
Combined	**Combined analysis using 1-3 and 5**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]		[redacted]		£17,327

Applying the various assumptions uni-variately to the model gives an ICER in the range of £14,788 to £27,916. Applying analyses 1 to 3 to the model, whilst applying the exacerbation rates in SoC to be be equal to SoC pre-trial rates in MENSA (analysis 5), gives a combined ICER of £17,327 per QALY gained, as shown in Table 9.

2.4 *Analysis 3: blood eosinophil level ≥300 cells/µl in the last year, and need continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)*

For the reasons above and in section 1, data is provided on the clinical, (Table 10, Table 11 and Table 12) and cost-effectiveness in an SREA population with the higher blood eosinophil threshold of ≥300 cells/µl in the past year (baseline or historic), and need continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year).

Table 10 Efficacy results for proposed population (≥300 cells/µl in the last year, and need continuous or frequent treatment with oral corticosteroids) for DREAM, MENSA and SIRIUS

		Proposed Population with ≥300 cells/µL with ≥4 exacerbations or mOCS																	
		ITT				DREAM				ITT			MENSA			ITT		SIRIUS	
		Pbo	75mg IV	250mg IV	750mg IV	Pbo	75mg IV	250mg IV	750mg IV	Pbo	100mg SC	75mg IV	Pbo	100mg SC	75mg IV	Pbo	100mg SC	Pbo	100mg SC
Rate of Clinically Significant Exacerbations	n	155	153	152	156	55	52	52	53	191	194	191	68	94	82	66	69	53	61
	Exacerbation rate/year	2.4	1.24	1.46	1.15	2.87	1.19	1.26	1.17	1.74	0.83	0.93	2.58	1.45	1.21	2.12	1.44	2.29	1.38
Comparison vs placebo	Rate ratio		0.52	0.61	0.48		0.42	0.44	0.41		0.47	0.53		0.56	0.47		0.68		0.60
	95% CI		0.39, 0.69	0.46, 0.81	0.36, 0.64		0.27, 0.64	0.29, 0.67	0.26, 0.63		0.35, 0.64	0.40, 0.72		0.37, 0.85	0.30, 0.73		0.47, 0.99		0.40, 0.90
	p value		<0.001	<0.001	<0.001		<0.001	<0.001	<0.001		<0.001	<0.001		0.006	<0.001		0.042		0.014
Rate of Exacerbations requiring Hospitalisation or ED visits	n	155	153	152	156	55	52	52	53	191	194	191	68	94	82	66	69	53	61
	Exacerbation rate/year	0.43	0.17	0.25	0.22	0.46	0.23	0.27	0.21	0.2	0.08	0.14	0.44	0.25	0.12	0.22	0.08	0.25	0.09
Comparison vs placebo	Rate ratio		0.4	0.58	0.52		0.50	0.60	0.45		0.39	0.68		0.58	0.28		0.35		0.37
	95% CI		0.19, 0.81	0.30, 1.12	0.27, 1.02		0.18, 1.41	0.23, 1.55	0.16, 1.27		0.18, 0.83	0.33, 1.41		0.24, 1.39	0.09, 0.81		0.09, 1.40		0.09, 1.46
	p value		0.011	0.106	0.056		0.188	0.293	0.133		0.015	0.299		0.22	0.019		0.136		0.154
Rate of Exacerbations requiring Hospitalisation	n	155	153	152	156	55	52	52	53	191	194	191	68	94	82	Due to insufficient events no analysis of hospitalisation rate could be performed			
	Exacerbation rate/year	0.18	0.11	0.12	0.07	0.24	0.17	0.18	0.08	0.1	0.03	0.06	0.32	0.09	0.05				
Comparison vs placebo	Rate ratio		0.61	0.65	0.37		0.69	0.72	0.34		0.31	0.61		0.29	0.16				
	95% CI		0.28, 1.33	0.31, 1.39	0.16, 0.88		0.22, 2.21	0.25, 2.10	0.09, 1.27		0.11, 0.91	0.23, 1.66		0.07, 1.23	0.03, 0.89				
	p value		0.214	0.268	0.025		0.534	0.551	0.108		0.034	0.334		0.094	0.036				
SGRQ	n	SGRQ was not an endpoint in DREAM								177	184	174	64	91	73	61	65	48	58
	LS Mean (SE)									37.7 (1.16)	30.7 (1.13)	31.2 (1.16)	40.9 (2.04)	33.2 (1.71)	33.3 (1.92)	44.3 (1.73)	38.5 (1.68)	44.8 (2.07)	38.0 (1.87)
	LS Mean Change (SE)									-9.0 (1.16)	-16.0 (1.13)	-15.4 (1.16)	-9.4 (2.04)	-17.1 (1.71)	-10.0 (1.92)	-3.1 (1.73)	-8.8 (1.68)	-2.6 (2.07)	-9.3 (1.87)
Comparison vs placebo	Difference										-7	-6.4		-7.7	-7.6		-5.8		-6.7
	95% CI										-10.2, -3.8	-9.7, -3.2		-13.0, -2.5	-13.2, -2.1		-10.6, -1.0		-12.3, -1.1
	p value										<0.001	<0.001		0.004	0.007		0.019		0.019
ACQ[1]	n	121	127	126	129	41	45	42	41	170	173	161	62	88	69	53	58	53	58
	LS Mean (SE)	1.72 (0.087)	1.56 (0.087)	1.45 (0.086)	1.52 (0.086)	1.85 (0.74)	1.71 (0.175)	1.43 (0.178)	1.45 (0.176)	1.7 (0.069)	1.26 (0.068	1.28 (0.070)	1.97 (0.114)	1.32 (0.097)	1.4 (0.108)	1.98 (0.128)	1.46 (0.126)	1.98 (0.128)	1.46 (0.126)
	LS Mean Change (SE)	-0.59 (0.087)	-0.75 (0.087)	-0.87 (0.086)	-0.80 (0.086)	-0.62 (0.74)	-0.77 (0.175)	-1.05 (0.178)	-1.03 (0.176)	-0.50 (0.069)	-0.94 (0.068)	-0.92 (0.070)	-0.37 (0.114)	-1.02 (0.097)	-0.94 (0.108)	-0.09 (0.128)	-0.61 (0.126)	-0.09 (0.128)	-0.61 (0.126)
Comparison vs placebo	Difference		-0.16	-0.27	-0.2		-0.15	-0.43	-0.40		-0.44	-0.42		-0.65	-0.57		-0.52		-0.52
	95% CI		-0.39, 0.07	-0.51, -0.04	-0.43, 0.03		-0.62, 0.33	-0.90, -0.04	-0.88, 0.07		-0.63, -0.25	‘-0.61, -0.23		-0.95, -0.36	-0.88, -0.26		-0.87, -0.17		-0.87, -0.17
	p value		0.183	0.02	0.085		0.543	0.076	0.097		<0.001	<0.001		<0.001	<0.001		0.004		0.004

Table 11 Meta-analysis efficacy results for proposed population ≥300 cells/µl in the last year, and need continuous or frequent treatment with oral corticosteroids) for DREAM, MENSA and SIRIUS

		ITT population[2]			≥300 cells/µL with ≥4 exacerbations or mOCS					
		Meta-analysis of DREAM and MENSA			Meta-analysis of DREAM and MENSA			Meta-analysis of DREAM, MENSA plus SIRIUS		
		Pbo	75mg IV / 100mg SC	All Doses	Pbo	75mg IV / 100mg SC	All Doses	Pbo	75mg IV / 100mg SC	All Doses
Rate of Clinically Significant Exacerbations Comparison vs placebo	n	346	538	846	123	228	333	176	289	394
	Rate ratio		0.51	0.53		0.47	0.46		0.51	0.50
	95% CI		0.42, 0.62	0.44, 0.62		0.36, 0.62	0.36, 0.59		0.01, 0.64	0.40, 0.61
	p value		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001
Rate of Exacerbations requiring Hospitalisation or ED visits Comparison vs placebo	n	346	538	846	123	228	333	176	289	394
	Rate ratio		0.53	0.60		0.46	0.48		0.44	0.46
	95% CI		0.33, 0.84	0.40, 0.89		0.24, 0.89	0.27, 0.86		0.25, 0.80	0.27, 0.79
	p value		0.007	0.012		0.021	0.013		0.007	0.004
Rate of Exacerbations requiring Hospitalisation Comparison vs placebo	n	346	538	846	123	228	333	Due to insufficient events in SIRIUS no analysis could be performed		
	Rate ratio		0.50	0.49		0.44	0.44			
	95% CI		0.28, 0.89	0.30, 0.81		0.18, 1.05	0.21, 0.94			
	p value		0.018	0.005		0.066	0.033			
SGRQ[3] Comparison vs placebo	n	No analysis possible as no SGRQ results in DREAM			No analysis possible as no SGRQ results in DREAM			112	149	222
	Difference								-7.3	-7.3
	95% CI								-11.1, -3.5	-10.9, -3.7
	p value								<0.001	<0.001
ACQ[4] Comparison vs placebo	n	298	465	732	121	219	322	174	279	382
	Difference		-0.34	-0.29		-0.50	-0.52		-0.53	-0.54
	95% CI		-0.48, -0.20	-0.42, -0.17		-0.73, -0.27	-0.74, -0.30		-0.73, -0.33	-0.74, -0.35
	p value		<0.001	<0.001		<0.001	<0.001		<0.001	<0.001

Table 12 OCS reduction results for proposed population (≥300 cells/µl in the last year, and need continuous or frequent treatment with oral corticosteroids) for SIRIUS

		SIRIUS			
		ITT		≥300 cells/µL with ≥4 exacerbations or mOCS	
		Pbo	100mg SC	Pbo	100mg SC
% OCS reduction during week 20-24	90% - 100**% (%)**	7(11)	4 (8)	7(11)	16 (23)
	75% - <90% **(%)**	5 (8)	4 (8)	5 (8)	12 (17)
	50% - <75% **(%)**	10 (15)	7 (13)	10 (15)	9 (13)
	>0% - <50% **(%)**	7 (11)	5 (9)	7 (11)	7 (10)
	No change or any increase or lack of asthma control or withdrawal from treatment (%)	37 (56)	33 (62)	37 (56)	25 (36)
Comparison vs placebo	Odds Ratio to Placebo				2.39
	95% CI				1.25, 4.56
	p-value				0.008

		SIRIUS			
		ITT		≥300 cells/µL with ≥4 exacerbations or mOCS	
		Pbo	100mg SC	Pbo	100mg SC
≥50% Reduction in Daily OCS Dose, n (%)	n	66	53	53	69
	50% to 100%	22 (33)	15 (28%)	15 (28%)	37 (54)
	<50%, no decrease in OCS, lack of asthma control, or withdrawal from treatment	44 (67)	38 (72%)	38 (72%)	32 (46)
Comparison vs placebo	Odds ratio to placebo				**2.26**
	95% CI				1.10, 4.65
	p-value				0.027
Reduction in Daily OCS Dose to ≤5 mg, n (%)	n	66	53	53	69
	Reduction to ≤5 mg	21 (32)	15 (28%)	15 (28%)	37 (54)
	Reduction to >5 mg, lack of asthma control, or withdrawal from treatment	45 (68)	38 (72%)	38 (72%)	32 (46)
Comparison vs placebo	Odds ratio to placebo				**2.45**
	95% CI				1.12, 5.37
	p-value				0.025
Total Reduction of OCS Dose, n (%)	n	66	53	53	69
	Total (100%) reduction (0 mg)	5 (8)	2 (4%)	2 (4%)	10 (14)
	OCS taken, lack of asthma control, or withdrawal from treatment	61 (92)	51 (96%)	51 (96%)	59 (86)
Comparison vs placebo	Odds ratio to placebo				**1.67**
	95% CI				0.49, 5.75
	p-value				0.414
Median Percentage Reduction in Daily OCS Dose	n	66	53	53	69
	Median (%)	0.0	0.0	0.0	50.0
	95% CI of the median	-20.0, 33.3	-50, 20	-50, 20	20.0, 75.0
	Median difference				**-30.0**
Comparison vs placebo	95% CI of the median difference				-66.7, 0.0
	p-value				0.007

Looking at the clinical efficacy data in the exacerbation studies MENSA and DREAM for a population with ≥300 cells/µL in the past year and a need for continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year), it can be seen that the data shows a small improvement compared to the ITT population, with a 44% to 59% statistically and clinically significant reduction in exacerbation rate (vs. 39% to 53% ITT). While the relative rate of clinically significant exacerbations remains consistent between the ITT population and proposed population in the exacerbation studies DREAM and MENSA the absolute rate reduction is improved. Demographics for this sub-group can be found in appendix 1.

There is a noticeably greater improvement in exacerbation rate in patients on continuous OCS (i.e. SIRIUS population) of 40% (p=0.042) vs. 32% (p=0.014) in the ITT. This trend can also be observed when looking at OCS dose reduction in SIRIUS. By introducing a threshold of ≥300 cells/µL in the past year (baseline or historic) the odds of achieving an OCS reduction improved from 2.39 (p=0.008) in the ITT population to 3.51 (p<0.001). There were also greater, statistically significant odds of achieving a dose reduction by ≥50% and to ≤5mg. The median difference increased from 30% (p=0.007) in the ITT to 50% (p<0.001) in this sub-group. This greater improvement could also be observed compared to the subgroup in analysis 2 (continuous or frequent treatment with oral corticosteroids).

Patients on maintenance OCS may have suppressed eosinophil levels, thus by selecting patients with a blood eosinophil threshold of ≥300 cells/µL in the previous 12 months, arguably a more severe asthma patient population is identified with higher eosinophilic inflammation despite oral corticosteroid use. The above data supports this argument and highlights the additional clinical benefit patients receive from mepolizumab treatment when identified by a blood eosinophil threshold of ≥300 cells/µL.

For ease of comparison the base case results are using the assumptions that were used in our original submission, together with 6 sensitivity analyses that reflect the discussions in the Committee, as well as alternative assumptions post Continuation Criteria, to assess how the ICER varies when different assumptions are applied to the model (seeTable 13).

Table 13 Results of analysis 3: blood eosinophil level ≥300 cells/µl in the last year, and need for continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year), base case and scenario analyses (with PAS)

Sensitivity analysis		GSK sub-population				
		Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)
N/A	**Base-case**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£22,134
1	**Direct EQ-5D scores**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£28,949
2	**Lifetime treatment duration**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£22,363
3	**Duration of an exacerbation from MENSA rather than Lloyd**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£22,674
4	**CC exacerbation rate from COSMOS (1.02), SOC MENSA in-trial (2.58)**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£24,273
5	**Post CC rate from COSMOS (1.02), SOC MENSA pre-trial (5.20)**					

	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£14,149
6	**Post CC rate (1.02) and SOC set to non-responders from COSMOS (5.26)**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£14,043
Combined	**Combined analysis using 1-3 and 5**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£16,798

Applying the various assumptions uni-variately to the model gives an ICER in the range of £14,043 to £28,949 per QALY gained. Applying analyses 1 to 3 to the model, whilst allowing the exacerbation rates in the SoC arm to be equal to SoC pre-trial rates in MENSA (analysis 5), gives a combined ICER of £16,798 per QALY gained, as shown in Table 13.

We acknowledge that the ICERs resulting from this sub-population are only marginally improved compared to those based purely on the history of exacerbations (or requirement for frequent courses of oral corticosteroids). This is consistent with the finding that in SREA the blood eosinophil level is a predictor of disease severity (i.e. those patients with a greater exacerbation history will also have a higher eosinophil count, demonstrating more severe disease). However as clinicians have fed back to us that they would wish to consider eosinophil level when identifying appropriate patients for treatment we felt it was important to present this evidence to the committee and that this could form the basis of guidance by NICE. Moreover, our sub-group data have shown that maintenance OCS patients have additional clinical benefit from mepolizumab treatment when identified by a blood eosinophil threshold of ≥300 cells/µL.

In summary, given the clinical and cost effectiveness data presented, GSK believes that mepolizumab should be approved for guidance, which could be worded as:

Who can have mepolizumab?

You should be able to have mepolizumab if you:

- have been diagnosed with severe refractory eosinophilic asthma,
- and need continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)
- and have blood eosinophils ≥300 cells/µl in the last year

2.5 *Consideration of previous omalizumab users*

In the ACD the committee recommended that guidance could not be issued with respect to patients previously treated with omalizumab as there were no data available in this population.

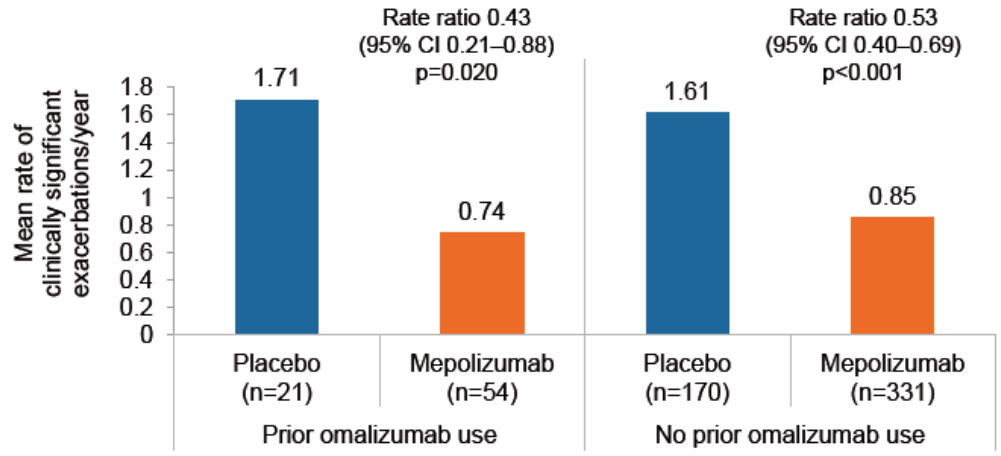
Previous omalizumab user data were presented in the company submission. Patients previously on omalizumab were included in the clinical trial program for mepolizumab. Patients were allowed to have been treated previously with omalizumab in the phase III trials as long as there was an interval of 130 days for safety reasons and to allow adequate washout (i.e. no possible interference in efficacy) (page 45, table 11 of the CS). In the phase III trials, 20% of patients in MENSA and 36% in SIRIUS of the total proposed population had received omalizumab previously (page 69 of 282, Table 17 & page 71, Table 18 of Company Submission).

Section 4.8.1.7 of our submission states that: '*The number of subjects [of ITT MENSA population] 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*.' Table 48 in the company submission presents the efficacy results in previous omalizumab users vs. naive patients. While subject numbers of previous omalizumab users were small, efficacy was comparable to omalizumab naive patients in the 100mg SC group.

In addition, new clinical data are now available (Figure 7), which show that in people with severe refractory eosinophilic asthma, independent of being on omalizumab previously (>130 days), patients treated with mepolizumab demonstrated a significant reduction in exacerbations in MENSA (prior users [n=54]: RR 0.74, p=0.02 & non-prior users [n=331]: RR 0.85, p<0.001) and a comparable reductions in OCS use (prior users [n=23]: OR 2.15, p=0.197 & non-prior users [n=46]: RR 2.33, p=0.021); as well as a comparable adverse event profile (11;12).

These data show that there is no evidence of differential effectiveness in people previously treated with omalizumab, and as such, there is no reason to exclude patients from guidance who have received omalizumab previously.

Figure 7 Exacerbation rate by prior omalizumab use (MENSA ITT)



CI, confidence interval

3 Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Within the ACD, we feel there have been some misinterpretations of our evidence, our licence, and previous NICE guidance, which may have led to confusion or ambiguity around our key clinical and cost effectiveness arguments in addition to those already covered in answer to Questions 1 and 2. The key points which we feel require clarification have been identified and outlined below, as well as a list of factual inaccuracies found within the ACD document.

3.1 *The comparison with SoC*

3.1.1 Increased efficacy with mepolizumab with increase blood eosinophil levels in SREA

In section 4.4 of the ACD, the Committee states that '*The evidence review group (ERG) comment that in the company's analysis, the reduction in exacerbations with mepolizumab was greater in people with a blood eosinophil count below 300 cells/µL compared with those with 300 cells/µL or more. The clinical experts stated that this was counterintuitive*.' We agree with the clinical experts that this would be counterintuitive but would like to point out that this statement is incorrect.

In the SmPC, section 5.1 table 3 (combined DREAM and MENSA trial population [75mg IV and 100mgSC, n=538]) the rate ratio for rate of clinically significant exacerbations by blood eosinophil count in mepolizumab vs. placebo shows that there is an increased reduction in exacerbation rate with increased eosinophil levels at screening (150 to <300 cells/µL: RR 0.72 [CI 0.47, 1.1] vs. 300 to <500 cells/µL: 0.62 [CI 0.41, 0.93]). Indeed in the company submission (section 4.9, page 106) it can be seen that in phase III study MENSA the rate ratios for reduction in exacerbations are 0.48 for 100mg SC mepolizumab in both 150 to <300 cells/µL and 300 to <500 cells/µL sub-groups.

This has been confirmed by more recent results from a pooled analysis of 2 RCTs ITT population (DREAM and MENSA), which show improvements in exacerbation rates, as well as asthma control and SGRQ, with higher baseline eosinophil levels. (13)

We believe the confusion arose as the phase III studies differentiate between historic and 'at screening' blood eosinophil levels as a marker of response. 'At screening' blood eosinophil levels have been found to be a better predictor of response (i.e. patients selected at ≥150 cells/µL at initiation had a better rate ratio compared to patients that entered the trial by ≥300 cells/µL in the last 12 months). Patients had to fulfill one of the two inclusion criteria: ≥150 cells/µL at screening or ≥300 cells/µL in the last 12 months. Patients in MENSA who entered the study with <300 cells/µL in the last 12 month therefore by definition had to have ≥150 cells/µL at screening. As the screening blood eosinophil level was found to be a better marker of response it is therefore logical that patients with <300 cells/µL in the last 12 month but a screening level of ≥150 cells/µL did better than those with a historic blood eosinophil level of ≥300 cells/µL in the last 12 months. This is different to comparing blood eosinophil levels at a specific point in time at screening.

3.1.2 Accuracy of NICE guidance for omalizumab in the ACD

There is an inaccuracy in section 3.17 and 3.18 that states that the guidance for omalizumab is for use in patients with 2 or more exacerbations. This appears to have caused some confusion elsewhere regarding the appropriateness of the GSK proposed sub-grouping according to ≥4 exacerbations.

Note the guidance for TA278 reads: '*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).***'

3.2 *The comparison with Omalizumab*

3.2.1 Appropriate evidence for exacerbation rate for this comparison

In section 3.49, the ERG also carried out the following scenario analyses: using the exacerbation rates ratios based on people on maintenance oral corticosteroids only from the SIRIUS study. However as discussed, consistent with the existing omalizumab NICE guidance, the patient population should include patients receiving frequent courses as well as maintenance OCS. Thus the GSK proposed population from MENSA supported by DREAM is the most appropriate for comparison to the omalizumab NICE reimbursement population as this includes patients receiving frequent courses and continuous OCS . Thus this ERG scenario analysis of the NMA is not a valid scenario for consideration for guidance.

3.2.2 Comparison of mepolizumab vs. omalizumab OCS sparing effectiveness

Section 3.46 in the ACD states that "*14.5% of patients stopped oral corticosteroids treatment in SIRIUS compared with 41.9% of those whose disease responded to omalizumab in the technology appraisal*."

However, it is important to note that the 41.9% figure is not the proportion of ITT patients in EXALT who stop OCS. Rather, only 22% of patients in EXALT are maintenance OCS patients at baseline. Of those 22%, 76.8% are deemed to be "responders" on the Global Evaluation of Treatment Effectiveness (GETE) questionnaire. Of those responders, 41.9% cease taking maintenance OCS. Maintenance of asthma control in those patients is not reported (14).

Conversely, the SIRIUS trial was set up as a phase III double-blind randomised control trial for which steroid sparing were the primary and secondary endpoints. In the SIRIUS trial 14.1% of patients were able to cease mOCS whilst maintaining asthma control.

In addition, in TA278 for omalizumab, the Assessment Group report clearly states that evidence that omalizumab treatment reduced OCS use was limited: the OCS maintenance subgroup of EXALT showed statistically significant benefits; this was not found in a subgroup of one other RCT in controlled patients. The Assessment Group highlights several other limitations with the steroid sparing evidence for omalizumab in their report that are not reflected in the mepolizumab ACD conclusion.

It is a misrepresentation to compare the 41.9% and 14.1% figures side by side and there is uncertainty as to the extent of the steroid sparing effectiveness of omalizumab.

3.3 Factual inaccuracies

Description of inaccuracy	Description of proposed amendment	Justification for amendment
Section.3.1: People having mepolizumab were more likely to reduce their dose of corticosteroids compared with placebo with an odds ratio (OR) of 2.39 (95% confidence interval [CI] 1.25 to 4.56) in the modified ITT population, 1.81 (95% CI 0.86 to 3.79) in the proposed population, and 2.75 (95% CI 0.72 to 10.59) in the restricted population. None of these results were statistically significant.	Suggest changing this to: "In the mITT population this result was statistically significant, while in the proposed and restricted population it did not reach significance (0.115 and 0.14, respectively)."	Factual inaccuracy as SIRIUS primary endpoint in the mITT was statistically significant.
Section 3.3 states "The population included people aged 12 years and older with severe refractory eosinophilic asthma on high-dose oral corticosteroids and a history of 2 or more exacerbations in the previous 12 months." Section 3.4 states : The inclusion criteria were similar to MENSA, including people aged 12 years and older with severe refractory eosinophilic asthma on high-dose oral corticosteroids and a history of 2 or more exacerbations in the previous 12 months."	This should read ""The population included people aged 12 years and older with severe refractory eosinophilic asthma on high-dose inhaled corticosteroids and a history of 2 or more exacerbations in the previous 12 months." This should read ""The inclusion criteria were similar to MENSA, including people aged 12 years and older with severe refractory eosinophilic asthma on high-dose inhaled corticosteroids and a history of 2 or more exacerbations in the previous 12 months."	Factual inaccuracy as people in MENSA were on high dose ICS, not necessarily high dose OCS.
3.9 Table 3 contains an inaccuracy. The 'restricted population' did include patients on systemic corticosteroids but they would have required ≥4 exacerbations in the previous 12 months to be included in the analyses.	The sentence should read, "But, the company presented further analyses that excluded patients on systemic corticosteroids that had <4 exacerbations."	Factual inaccuracy: The 'restricted population' did include patients on OCS but they would have required >=4 exacerbations to be included. The ACD states that the restricted population excludes OCS – this is factually incorrect.
Section 3.10: "But, the injection-site reactions was higher for mepolizumab given subcutaneously (8%) than intravenously (1.7%)."	1.7% is incorrect. The sentence should therefore read, "But, the injection-site reactions was higher for mepolizumab given subcutaneously (8%) than intravenously (3%)."	Factual inaccuracy as the figure of 1.7% is incorrect. The percentage of injection-site reactions in the IV arm was actually 3%.
3.11 Results in the ITT were statistically significant; therefore the last sentence of this paragraph is factually incorrect	Please remove the last sentence of this paragraph or state that "The results of the modified ITT population were statistically	Factual inaccuracy: Results in the ITT were statistically

'None of these results were statistically significant.'	significant."	significant
3.13 states, "The company highlighted that at baseline, about one third of patients in DREAM reported an EQ-5D utility score of 1.0, which it considered did not reflect the impact of severe asthma on quality of life and also meant that for this group of patients, quality of life could not improve with mepolizumab treatment."	It should read, "The company highlighted that at baseline, about one third of patients in DREAM reported an EQ-5D utility score of 1.0, which it considered did not reflect the impact of severe asthma on quality of life and also meant that for this group of patients, an improvement in quality of life from mepolizumab treatment could not be adequately captured."	It's not that patients could not improve on mepolizumab it's that this improvement could not be captured with EQ-5D due to the ceiling effects seen in this instrument.
3.28 Disutilities are written without a "-" negative sign	Please add a "-"negative sign, it should read -0.10 and -0.20.	Disutilities should be referred do as with a - sign
3.33 The ACD states "...the company estimated the dose-dependent risk of developing 6 adverse events associated with systemic corticosteroid therapy: myocardial infarction; glaucoma; diabetes mellitus; cataracts; osteoporosis; and peptic ulcer."	There were only 5 adverse events modelled; remove glaucoma. Statement should read "...the company estimated the dose-dependent risk of developing 5 adverse events associated with systemic corticosteroid therapy: myocardial infarction; diabetes mellitus; cataracts; osteoporosis; and peptic ulcer."	Incorrectly states an additional adverse event
3.36 Currently states, "The ERG also considered that given the concerns over differences between studies, a random-effects model would be more appropriate than a fixed-effect model for all scenarios and endpoints."	Should state, "The ERG also considered that given the concerns over difference between studies, the random –effects model provided would be more appropriate than the fixed-effect model for all scenarios and endpoints".	The way the statement is written it implies that only a fixed-effect model was provided
Section 4.8: The committee noted that mepolizumab, compared with placebo, was associated with a lower rate of clinically significant exacerbations in all trials, but these results were less pronounced and not statistically significant in the SIRIUS trial	Suggest changing this to: "The committee noted that mepolizumab compared with placebo, was associated with a lower rate of clinically significant exacerbations in all trials, but were still statistically significant in the mITT (p=0.042)"	Factual inaccuracy as SIRIUS endpoint of reduction in exacerbations was statistically significant.

4 Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion, or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

4.1 *Age*

In our response to the ACD we have presented evidence to support that the age used in our model is representative of English clinical practice. Non-guidance on the basis that a small number of patients at either extreme of the age distribution may be less cost effective runs the risk of depriving the target population and we believe would be inequitable. It would therefore be most appropriate to base guidance on the results from the trial population, which are generalisable to the English population, and are most likely to receive this medicine.

Reference List

(1) Sweeney J, Patterson CC, Menzies-Gow A, Niven R. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. Thorax 2016 Jan 27;71:339-46.

(2) Yancey S, Myer B, Gunsoy N, Keene O. Exacerbation Reduction in Severe Eosinophilic Asthma Based on Eosinophil Thresholds. Journal of Allergy and Clinical Immunology 16 A.D. Feb 1;AB208.

(3) Bel EH, Sousa A, Fleming L, Bush A. Diagnosis and definition of severe refractory asthma:an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax 2011;66:910-7.

(4) Roberts NJ, Lewsey JD, Gillies M, Briggs AH, Belozeroff V, Globe DR, et al. Time trends in 30 day case-fatality following hospitalisation for asthma in adults in Scotland: a retrospective cohort study from 1981 to 2009. Respir Med 2013 Aug;107(8):1172-7.

(5) Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. Respir Med 2007 Aug;101(8):1659-64.

(6) GSK. COSMOS: 115661; A multi-centre, open-label, long-term safety study of mepolizumab in asthmatic subjects who participated in the MEA115588 or MEA115575 trials. 2015 Jul 17.

(7) Haldar P, Brightling CE, Singapuri A, Hargadon B, Gupta S, Monteiro W, et al. Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. J Allergy Clin Immunol 2014 Mar;133(3):921-3.

(8) Heaney et al. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. Thorax 65, 787-794. 2010.

(9) Price DB, et al. Blood eosinophilic count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir.Med. 3, 849-858. 2015.

(10) Robert Y. The Identification and Description of Severe Asthma Patients in a Cross-Sectional Study, the Ideal Study. J.Allergy Clin Immunol. 137[Supplement 2]. 2016.

(11) Albers, Bourdin A, Price R, Yancey S. Effect of mepolizumab in severe eosinophilic asthma patients with history of omalizumab treatment. Journal of Allergy and Clinical Immunology 2015 Feb 1;135(2):AB383.

(12) Prazma CM, Megnan A, Price R, Ortega H. Effect of Mepolizumab in OCS Dependent Severe Eosinophilic Asthma Patients with History of Omalizumab. Journal of Allergy and Clinical Immunology 2015 Feb 1;135(2):AB383.

(13) Yancey S, Mayer B, Gunsoy N. Exacerbation Reduction in Severe Eosinophilic Asthma Based on Eosinophil Thresholds. Journal of Allergy and Clinical Immunology 2016 Feb 1;137(2):AB208.

(14) Bousquet J, Siergiejko Z, Swiebocka E, Humbert M. Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. Allergy 2011;66:671-8.

Appendix 1: Patient demographics for analysis 2 and 3

Table 14 Baseline Characteristics for individual trials (DREAM, MENSA, SIRIUS) for sub-groups: ***continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)****and* ***blood eosinophil level ≥300 cells/µl in the last year, and need continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)***

		DREAM						**MENSA**				**SIRIUS**			
		≥4 exacerbations or mOCS			**≥300 cells/µL in the past year with ≥4 exacerbations or mOCS**			**≥4 exacerbations or mOCS**		**≥300 cells/µL in the past year with ≥4 exacerbations or mOCS**		**≥4 exacerbations or mOCS**		**≥300 cells/µL in the past year with ≥4 exacerbations or mOCS**	
Characteristic	**Analysis**	Placebo	Mepo 75IV/100mg SC	All doses	Placebo	Mepo 75IV/100mg SC	All doses	Placebo	Mepo 75IV/100mg SC	Placebo	Mepo 75IV/100mg SC	Placebo	Mepo 100mg SC	Placebo	Mepo 100mg SC
Age (yrs)	**n**	66	70	212	55	52	157	77	190	68	176	66	69	53	61
	Mean	49.2	52.5	50.7	49.5	51.0	49.7	47.7	52.2	49.2	52.4	49.9	49.8	50.9	48.7
	SD	10.56	10.44	11.13	10.29	10.62	11.41	14.37	13.09	13.60	13.35	10.30	14.10	10.0	13.71
	Median	51.0	52.0	52.0	51.0	51.0	51.0	48.0	53.5	49.0	55.0	51.0	53.0	53.0	51.0
	Min.	23	24	15	23	24	15	12	12	12	12	28	16	28	16
	Max.	67	69	73	67	69	73	73	82	73	82	70	74	69	70
Sex	**n**	66	70	212	55	52	157	77	190	68	176	66	69	53	61
	Female	40 (61%)	50 (71%)	136 (64%)	33 (60%)	35 (67%)	98 (62%)	41 (53%)	111 (58%)	36 (53%)	101 (57%)	30 (45%)	44 (64%)	25 (47%)	39 (64%)
	Male	26 (39%)	20 (29%)	76 (36%)	22 (40%)	17 (33%)	59 (38%)	36 (47%)	79 (42%)	32 (47%)	75 (43%)	36 (55%)	25 (36%)	28 (53%)	22 (36%)
Ethnicity	**n**	66	70	212	55	52	157	77	190	68	176	66	69	53	61
	Hispanic or Latino	6 (9%)	5 (7%)	16 (8%)	5 (9%)	4 (8%)	13 (8%)	4 (5%)	13 (7%)	2 (3%)	12 (7%)	3 (5%)	2 (3%)	2 (4%)	2 (3%)
	Not Hispanic or Latino	60 (91%)	65 (93%)	196 (92%)	50 (91%)	48 (92%)	144 (92%)	73 (95%)	177 (93%)	66 (97%)	164 (93%)	63 (95%)	67 (97%)	51 (96%)	59 (97%)
Weight (kg)	**n**	66	70	212	55	52	157	77	190	68	176	66	69	53	61
	Mean	79.58	76.21	79.03	78.12	74.67	79.58	78.46	76.51	79.23	76.48	87.46	79.36	86.44	78.60
	SD	16.528	17.220	17.726	16.235	13.065	16.377	20.585	18.442	20.044	18.552	20.754	18.107	18.887	16.299
	Median	78.25	76.50	77.35	76.40	76.00	78.00	77.00	74.60	77.50	74.50	84.50	75.00	84.00	75.00
	Min.	53.0	45.0	45.0	53.0	45.0	45.0	45.0	45.0	45.0	45.0	55.0	47.0	57.0	47.0
	Max.	125.0	140.6	140.6	125.0	104.0	125.0	138.0	140.0	138.0	140.0	138.0	139.0	131.5	125.0
Duration of Asthma	**n**	66	70	212	55	52	157	77	190	68	176	66	69	53	61
	≥1 to <5 years	9 (14%)	7 (10%)	22 (10%)	8 (15%)	5 (10%)	14 (9%)	13 (17%)	20 (11%)	11 (16%)	19 (11%)	10 (15%)	7 (10%)	10 (19%)	6 (10%)
	≥5 to <10	15	12	36	13	10	29	11 (14%)	31 (16%)	10 (15%)	31 (18%)	9 (14%)	16	8 (15%)	15

	years	(23%)	(17%)	(17%)	(24%)	(19%)	(18%)						(23%)		(25%)
	≥10 to <15 years	12 (18%)	12 (17%)	34 (16%)	11 (20%)	8 (15%)	23 (15%)	11 (14%)	38 (20%)	9 (13%)	35 (20%)	8 (12%)	6 (9%)	4 (8%)	5 (8%)
	≥15 to <20 years	1 (2%)	7 (10%)	21 (10%)	1 (2%)	6 (12%)	16 (10%)	10 (13%)	18 (9%)	9 (13%)	16 (9%)	12 (18%)	11 (16%)	11 (21%)	10 (16%)
	≥20 to <25 years	9 (14%)	11 (16%)	29 (14%)	7 (13%)	8 (15%)	24 (15%)	7 (9%)	22 (12%)	5 (7%)	19 (11%)	5 (8%)	10 (14%)	3 (6%)	9 (15%)
	≥25 years	20 (30%)	21 (30%)	70 (33%)	15 (27%)	15 (29%)	51 (32%)	25 (32%)	61 (32%)	24 (35%)	56 (32%)	22 (33%)	19 (28%)	17 (32%)	16 (26%)
Airway Inflammation Characteristics:															
At visit 1 or documented in the previous 12 months elevated peripheral blood eosinophil count ≥300/uL	**Yes**	43 (65%)	42 (60%)	129 (61%)	43 (78%)	42 (81%)	129 (82%)	67 (87%)	171 (90%)	67 (99%)	171 (97%)				
	No	17 (26%)	17 (24%)	58 (27%)	7 (13%)	3 (6%)	14 (9%)	10 (13%)	19 (10%)	1 (1%)	5 (3%)				
	Unknown	6 (9%)	11 (16%)	25 (12%)	5 (9%)	7 (13%)	14 (9%)	0	0	0	0				
Baseline OCS daily dose (prednisolone equivalent) [2]	**n**	66	70	212	55	52	157	76	186	67	172	66	69	53	61
	0	21 (32%)	24 (34%)	69 (33%)	20 (36%)	20 (38%)	55 (35%)	33 (43%)	90 (47%)	27 (40%)	82 (47%)	0	0	0	0
	>0-<15 mg/day	27 (41%)	26 (37%)	82 (39%)	23 (42%)	18 (35%)	61 (39%)	30 (39%)	66 (35%)	28 (41%)	64 (36%)	39 (59%)	50 (72%)	31 (58%)	43 (70%)
	≥15 mg/day	18 (27%)	20 (29%)	61 (29%)	12 (22%)	14 (27%)	41 (26%)	13 (17%)	30 (16%)	12 (18%)	26 (15%)	27 (41%)	19 (28%)	22 (42%)	18 (30%)
	n	45	46	145	35	32	103	43	96	40	90	66	69	53	61
	Mean	16.38	17.25	17.78	14.32	18.55	17.55	15.09	12.31	15.29	12.13	13.21	12.36	12.87	12.34
	SD	12.328	13.533	17.979	9.702	15.158	19.013	14.905	10.225	15.356	10.486	6.261	7.173	5.664	7.372
	Median	10.00	10.00	10.00	10.00	11.25	10.00	10.00	10.00	10.00	10.00	12.50	10.00	12.5	10.0
	Min.	5.0	5.0	3.0	5.0	5.0	3.0	5.0	1.0	5.0	1.0	5.0	5.0	5.0	5.0
	Max.	60.0	60.0	160.0	50.0	60.0	160.0	80.0	50.0	80.0	50.0	35.0	35.0	30.0	35.0
Total number of exacerbations	**n**	66	70	212	55	52	157	77	190	68	176	66	69	53	61
	<2	0	0	0	0	0	0	0	0	0	0	21 (32%)	23 (33%)	20 (38%)	21 (34%)
	2	10 (15%)	11 (16%)	37 (17%)	8 (15%)	7 (13%)	23 (15%)	13 (17%)	60 (16%)	13 (19%)	27 (15%)	14 (21%)	9 (13%)	7 (13%)	7 (11%)
	3	19 (29%)	8 (11%)	36 (17%)	14 (25%)	3 (6%)	23 (15%)	9 (12%)	26 (14%)	7 (10%)	24 (14%)	11 (17%)	9 (13%)	9 (17%)	8 (13%)
	4+	37 (56%)	51 (73%)	139 (66%)	33 (60%)	42 (81%)	111 (71%)	55 (71%)	134 (71%)	48 (71%)	125 (71%)	20 (30%)	28 (41%)	17 (32%)	25 (41%)
	n	66	70	212	55	52	157	77	190	68	176	66	69	53	61
	Mean	5.56	5.37	5.00	5.44	5.81	5.17	5.39	5.04	5.35	5.09	2.92	3.35	2.81	3.34

	SD	5.271	4.001	3.570	4.590	4.415	3.666	3.588	2.945	3.582	2.924	2.759	3.395	2.632	3.473
	Median	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.0	4.0	2.0	3.0	2.00	3.00
	Min.	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	0.0	0.0	0	0
	Max.	30.0	25.0	25.0	26.0	25.0	25.0	19.0	21.0	19.0	21.0	13.0	16.0	12.0	16.0
Total number of exacerbations that required hospitalisation	**n**	66	70	212	55	52	157	77	190	68	176	66	69	53	61
	<2	57 (86%)	66 (94%)	194 (92%)	48 (87%)	49 (94%)	145 (92%)	63 (82%)	169 (89%)	55 (81%)	156 (89%)	63 (95%)	62 (90%)	50 (94%)	55 (90%)
	2	4 (6%)	3 (4%)	10 (5%)	3 (5%)	2 (4%)	6 (4%)	4 (5%)	14 (7%)	4 (6%)	13 (7%)	0	4 (6%)	0	3 (5%)
	3	3 (5%)	0	4 (2%)	2 (4%)	0	4 (3%)	5 (6%)	5 (3%)	5 (7%)	5 (3%)	2 (3%)	1 (1%)	2 (4%)	1 (2%)
	4+	2 (3%)	1 (1%)	4 (2%)	2 (4%)	1 (2%)	2 (1%)	5 (6%)	2 (1%)	4 (6%)	2 (1%)	1 (2%)	2 (3%)	1 (2%)	2 (3%)
Pre-bronchodilator % Predicted Normal FEV1 (%)	**n**	66	70	212	55	52	157	77	190	68	176	66	69	53	61
	Mean	55.5	57.9	58.5	56.5	57.6	59.2	60.7	58.7	58.7	59.0	57.8	59.6	58.6	58.3
	SD	16.82	16.87	17.47	16.89	17.90	17.77	19.27	18.19	18.85	18.57	18.54	17.04	17.61	17.24
	Median	54.1	58.7	57.9	54.9	61.7	59.7	58.9	56.9	56.2	57.4	58.7	61.5	60.4	59.5
	Min.	26	18	18	26	18	18	18	24	18	24	15	18	21	18
	Max.	102	94	108	102	94	108	109	128	109	128	93	94	93	94
Baseline Blood Eosinophils (U/mL)	**n**	66	70	212	55	52	157	77	188	68	174	66	69	53	61
	Geo. Mean	310	250	230	420	350	360	320	290	370	300	230	250	280	260
	Median	380	280	300	480	400	380	390	350	410	390	240	300	310	350
	Min.	0	0	0	0	100	0	0	0	0	0	0	0	0	0
	Max.	2300	1500	4100	2300	1500	4100	3000	2200	3000	2200	1800	2300	1800	2300
Baseline Total IgE (U/mL)	**n**	66	70	212	55	52	157	73	176	64	163	61	63	48	56
	Geo. Mean	137.13	140.02	130.95	174.29	166.11	154.63	110.00	152.05	98.66	155.20	114.07	117.22	115.34	122.45
	Median	168.00	152.50	135.00	181.00	104.50	149.00	126.00	166.00	116.00	167.00	1.312	1.247	112.00	106.50
	Min.	1.0	7.0	1.0	1.0	13.0	5.0	2.0	1.0	2.0	1.0	1.0	3.0	1.0	22.0
	Max.	3047.0	4114.0	9130.0	3047.0	1913.0	9130.0	11220.0	4880	11220.0	4880.0	3445.0	1487.0	2429.0	918.0
Baseline ACQ-5 Mean Score	**n**	65	67	206	54	50	153	77	185	68	171	66	69	53	61
	Mean	2.5	2.4	2.5	2.5	2.4	2.5	2.4	2.4	2.5	2.3	2.0	2.2	1.9	2.1
	SD	1.16	1.12	1.22	1.21	1.22	1.30	1.26	1.28	1.30	1.25	1.18	1.27	1.10	1.3
	Median	2.4	2.4	2.6	2.4	2.4	2.6	2.4	2.4	2.5	2.4	2.0	2.2	2.0	2.2
	Min.	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Max.	5	5	6	5	5	6	6	5	6	5	5	6	5	6
Baseline SGRQ Total Score	**n**							77	188	68	174	66	69	53	61
	Mean							51.7	50.6	51.7	49.9	45.0	49.6	43.9	50.6
	SD							18.87	18.93	19.46	18.41	18.38	17.81	18.23	17.95
	Median							53.2	52.0	52.6	51.3	44.7	49.7	43.4	54.1
	Min.							15	5	15	5	8	18	8	18
	Max.							95	90	95	90	81	98	77	98

Appendix 2: model input parameters for analyses 1-3 in section 2

Analysis 1 input parameters: ITT restricted to maintenance OCS

Exacerbation rates

Comparator	Annual rate	Cycle rate	Source
Mepolizumab + SOC: All patients	1.430	0.110	MENSA
Standard of Care	2.120	0.163	MENSA
End of trial: Exacerbation reduction	0.990	0.076	MENSA

Proportion of patients meeting continuation criteria

Continuation criteria	n	N	p	Source
End of trial: Exacerbation reduction	83	100	83.0%	MENSA

Distribution over the type of exacerbations

Exacerbation type	n	N	p	Source
Exacerbation: OCS burst	129	159	81.1%	MENSA
Exacerbation: ED visit	14	159	8.8%	MENSA
Exacerbation: Hospitalization	16	159	10.1%	MENSA

SGRQ utility values

Parameter	Value	Source
Mepo + SOC: all patients	0.747	MENSA
SOC: all patients	0.692	MENSA
Mepo + SOC: Exacerbation reduction	0.765	MENSA

EQ-5D utility values

Parameter	Value	Source
Mepo + SOC: all patients	0.768	DREAM
SOC: all patients	0.753	DREAM
Mepo + SOC: Exacerbation reduction	0.788	DREAM

Analysis 2 input parameters: continuous or frequent use of OCS (≥4 courses in last year)

Exacerbation rates

Comparator	Annual rate	Cycle rate	Source
Mepolizumab + SOC: All patients	1.360	0.105	MENSA
Standard of Care	2.740	0.211	MENSA
End of trial: Exacerbation reduction	0.770	0.059	MENSA

Proportion of patients meeting continuation criteria

Continuation criteria	n	N	p	Source
End of trial: Exacerbation reduction	170	190	89.5%	MENSA

Distribution over the type of exacerbations

Exacerbation type	n	N	p	Source
Exacerbation: OCS burst	230	287	80.1%	MENSA
Exacerbation: ED visit	29	287	10.1%	MENSA
Exacerbation: Hospitalization	28	287	9.8%	MENSA

SGRQ utility values

Parameter	Value	Source
Mepo + SOC: all patients	0.763	MENSA
SOC: all patients	0.699	MENSA
Mepo + SOC: Exacerbation reduction	0.778	MENSA

EQ-5D utility values

Parameter	Value	Source
Mepo + SOC: all patients	0.779	DREAM
SOC: all patients	0.780	DREAM
Mepo + SOC: Exacerbation reduction	0.800	DREAM

Analysis 3 input parameters: ≥300 eosinophils in last year and continuous or frequent use of OCS (≥4 courses in last year)

Exacerbation rates

Comparator	Annual rate	Cycle rate	Source
Mepolizumab + SOC: All patients	1.340	0.103	MENSA
Standard of Care	2.580	0.198	MENSA
End of trial: Exacerbation reduction	0.730	0.056	MENSA

Proportion of patients meeting continuation criteria

Continuation criteria	n	N	p	Source
End of trial: Exacerbation reduction	157	176	89.2%	MENSA

Distribution over the type of exacerbations

Exacerbation type	n	N	p	Source
Exacerbation: OCS burst	206	253	81.4%	MENSA
Exacerbation: ED visit	22	253	8.7%	MENSA
Exacerbation: Hospitalization	25	253	9.9%	MENSA

SGRQ utility values

Parameter	Value	Source
Mepo + SOC: all patients	0.773	MENSA
SOC: all patients	0.703	MENSA
Mepo + SOC: Exacerbation reduction	0.790	MENSA

EQ-5D utility values

Parameter	Value	Source
Mepo + SOC: all patients	0.797	DREAM
SOC: all patients	0.792	DREAM
Mepo + SOC: Exacerbation reduction	0.809	DREAM

Asthma UK

1. Has all of the relevant evidence been taken into account?

In making its draft guidance not to recommend mepolizumab for treating severe eosinophilic asthma, we do not believe that due consideration was given by the appraisal committee to the degree of morbidity that the severe asthma population often suffer which could be alleviated through this treatment.

As mentioned in our initial submission, people with severe asthma almost always find themselves taking very high doses of medicines for a long time and the side effects of these medicines, especially long-term oral corticosteroids (OCS), are often very serious. Use of OCS on a regular basis has well-documented side effects, including osteoporosis, psychological symptoms, Cushings syndrome, adrenal failure, diabetes, growth retardation, high blood pressure, cataracts and Addisons disease (Stuart et al 2005, www.ncbi.nlm.nih.gov/pubmed/15851433; Weldon 2009, www.ncbi.nlm.nih.gov/pubmed/19663120; Blackburn et al 2002, www.ncbi.nlm.nih.gov/pmc/articles/PMC1495107/).

While this was reiterated by the patient expert at the committee hearing, and acknowledged in the consultation document, we do not believe that the scale of this was fully considered. It is our view that the full economic costs of OCS use have not been and should be factored into the incremental cost-effectiveness ratio (ICER). People with severe asthma have to find a way to cope with persistent symptoms that can lead to lack of sleep, social isolation, feelings of despair and depression, low activity levels, weight gain and increased dependence on family and carers. The impact on everyday relationships was also described by the patient expert based on their own experience of severe asthma. Asthma UK also highlights this in our 2011 report Fighting for Breath:

> With the constant need to make compromises for severe asthma, relationships can suffer¦The impact of caring for someone with severe asthma is substantial " many parents struggle to maintain a job because their child needs their support. This doesnt just affect parents " other family members, or even children can also be carers. Sadly, because asthma isnt usually seen as something that has a big impact, those who spend a lot of time caring for people with severe asthma get even less recognition and support than other carers.

There was a key gap in the evidence considered. The impact on improving the quality of life of carers, and the quality of life benefits of reducing OCS were not captured in the model considered, which as highlighted by the appraisal committee would reduce the ICER of mepolizumab.

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

There is disagreement between the company and the ERG on the precise details of cost effectiveness modelling and the proposed population, but this is beyond the scope of Asthma UKs professional expertise.

However, we note that the European Medicines Agency stated that eosinophil levels were not sufficiently predictive to justify a specific cut-off within mepolizumabs marketing authorisation, but that the particular blood eosinophil threshold considered by NICE has a significant impact on the ICER. We believe this requires further consideration to enable modelling for a smaller patient population.

In addition, we believe there were flaws in placing omaluzimab as the comparator against mepolizumab, given that there is only a very small overlap of severe asthma patients that could benefit from both drugs. Omalizumab targets a completely different mechanism related to eosinophilic airway inflammation (Menzella et al 2015, www.ncbi.nlm.nih.gov/pmc/articles/PMC4323120) and is not an effective treatment option for the broader severe eosinophilic population. As such it is an inappropriate comparison. It is a novel treatment for an unmet need and there is no comparator as current treatment is substandard and ineffective with long-term side-effects.

Furthermore, feedback we have gathered from clinicians suggested that the St Georges Respiratory Questionnaire was a more appropriate method than EQ-5D for measuring improvements in quality of life for severe asthma patients due to it being able to effectively capture exacerbations (attacks).

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Asthma UK is deeply disappointed in the draft recommendation. Despite the appraisal committee agreeing that mepolizumab is an innovative treatment which meets an unmet need for severe eosinophilic asthma and is effective at reducing clinically significant exacerbations it is has not been recommended for use. This will result in people with severe eosinophilic asthma being unable to access a treatment that has shown clinical benefit in clinical trials. We would urge the appraisal committee to reconsider its interim decision on mepolizumab and instead recommend it for use for a smaller population of people with severe eosinophilic asthma.

As highlighted above, the provisional recommendations have also failed to take into account the impact on improving the lives of carers, and the health and quality of life benefits of reducing OCS were not captured in the model considered, which as highlighted by the appraisal committee would reduce the ICER. Without this included in the ICER the analysis is incomplete and warrants revisiting. We would therefore urge the appraisal committee to reconsider its provisional recommendations for mepolizumab. While we accept that there may be some doubt about the ICER, we believe that NICE and the company should consider innovative approaches to ensuring patient access to mepolizumab while issues concerning the ICER are addressed.

4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

As mentioned previously, there is a substantial unmet need for people with severe asthma in the treatment options available to them. People with severe asthma have very limited treatment options that involve high doses of drugs with toxic and damaging side effect profiles and significant long-term health impacts. Mepolizumab could provide an effective treatment option for people with severe eosinophilic asthma who currently have no treatment option. The rejection by the appraisal committee of this innovative treatment will mean people with severe eosinophilic asthma remain disadvantaged through a lack of access to effective treatments for their condition.

Asthma UK is deeply disappointed in the draft recommendation. With a significant unmet need and an estimated 250,000 people without effective treatment for severe asthma in the UK it is important that new treatments are made available to those for whom they are effective. By adding treatments to bespoke populations the unmet need can be reduced incrementally.

Due to the heterogeneity of asthma it is unlikely there will be effective universal treatments in the future and it will be essential to use objective tests in order to target appropriate subgroups with the

optimal effect. This will be fundamental to ensure that new, and inevitably costly, clinically-effective treatments are cost-effective.

Asthma UK firmly believes that the addition of mepolizumab is an important one, representing a step forward in the development of precision medicine for asthma. With the exception of a small overlap group who could be treated with omalizumab, mepolizumab provides a completely new targeted treatment option for a group who would otherwise have uncontrolled asthma with significant impact on their health including potentially life-threatening asthma attacks. "
Asthma UK welcomes the patient access scheme that the company has been agreed with the Department of Health. However, given that the conclusion of the ACD is that mepolizumab is not recommended for use on the NHS, Asthma UK strongly urges the company to negotiate with the Department of Health further. An appropriate price must be agreed so that mepolizumab can be given to those for whom it would be most beneficial on the NHS.
Asthma UK has consulted with a number of clinicians specialising in severe asthma and the consensus that we have gathered has been that a blood eosinophil level of 150 cells/microlitre is too low and that given the normal fluctuation of blood eosinophil levels it would not represent a high eosinophil level. We therefore recommend that the particular blood eosinophil threshold should be higher for those to ensure that this is more targeted to a population more likely to benefit from the treatment.

The long term impact of oral corticosteroids (OCS) must be fully considered in the cost effectiveness analysis of this treatment. As stated in our response to the consultation, and highlighted by the patient expert at the appraisal committee meeting, sustained OCS use has a significant impact on individual health. Recent studies have shown that OCS use can result in a higher prevalence of co-morbidities including type II diabetes and osteoperosis (Sweeney et al 2016, http://dx.doi.org/10.1136/thoraxjnl-2015-207630). This in turn has an impact on the NHS and any new treatment that will reduce use of OCS should take the long-term impact of OCS and subsequent costs into consideration.

In later comments from the ERG (3.3.45) it would appear that the full impact of reduced OCS use is not robust in their view. For a comprehensive cost-effectiveness analysis of any new severe asthma treatment the long-term impact of OCS use and the indicative reduction through trial data must be included. The acknowledgement that ˜the current analyses did not capture the impact on the ICER of reducing oral corticosteroid use (3.3.46) shows a fundamental failure of the cost-benefit modelling. From a patient perspective reduced OCS use is of prime importance. There are a number of treatments currently in development that we hope in the future will offer new options for some people with severe asthma, however these will never be cost-effective until the costs of OCS are fully considered in the model.

Exacerbations are equally important. Asthma attacks are life threatening and with a total in 2014 (the most recent data available) of 1216 deaths from asthma, reductions in exacerbations are an important outcome to consider when analysing the impact of potential new treatments. "
The use of the St Georges Respiratory Questionnaire, as collected within the MENSA and SIRIUS trials, would appear to be a better measure of quality of life than EQ-RD for the purpose of assessing treatments for severe asthma. Clinicians we sought feedback from ahead of this response thought that the St Georges Respiratory Questionnaire was more appropriate due to it being able to effectively capture exacerbations.

Asthma UK, having consulted with a number of clinicians, is of the opinion that the comparison between mepolizumab and omalizumab is inappropriate. The two treatments target different types of asthma and are for very different populations. Evidence shows that patients with severe asthma are comprised of complex, overlapping and non-overlapping phenotypes, including a severe eosinophilic asthma phenotype (Chung 2014, http://erj.ersjournals.com/content/43/2/343). Whilst there is a small overlap population (people with both allergic and eosinophilic severe asthma), mepolizumab should be used for people with eosinophilic asthma without effective treatment and therefore comparing the two treatments as though they could treat all cohorts is inaccurate and represents a significant flaw in NICEs assessment of this treatment. Whilst modelling was carried

out it should be noted by NICE that there is no viable comparator as mepolizumab is an innovative, novel treatment for a cohort without effective alternative treatment options. This needs to be reconsidered.

With regards to adverse events for mepolizumab, these appear to be acceptable based on the data presented. Patients with severe asthma constantly tell us that taking fewer OCS is of paramount importance to them, which was also one of the key points expressed by the patient expert at the appraisal committee meeting. The risk profile of mepolizumab appears to be acceptable.

As earlier stated the long term impact of OCS needs to be taken in to consideration. It is not clear to what extent comorbidities associated with OCS use have been assessed. Whilst standard care will be low in cost in the short term due to cheap OCS, the long term costs including comorbidities will be higher and should be factored in to the cost effectiveness model.

We consulted a number of expert clinicians involved in the treatment of severe asthma to help gain insights on the appropriate blood eosinophil level to set for the treatment of patients. There was broad agreement that the level of 150 cells/microlitre was set too low and as a result was not adequately targeted at the severe eosinophilic asthma population most likely to benefit. A blood eosinophil count of 300 cells/microlitre or more, as used within the DREAM trial, was considered to be a more appropriate definition of elevated eosinophilic airway inflammation.

This threshold would be more reflective of clinical practice, would more precisely target those with severe eosinophilic asthma likely to benefit from mepolizumab, and in turn would result in a lower ICER. By considering this treatment for those with a blood eosinophil count of 150 cells/microlitre, the assessment has been too broad with a resultant negative impact on the ICER.

Clinicians that we have consulted are mindful that this new treatment needs to be targeted effectively, and think that NICE should be reassured by the way that omalizumab has been introduced carefully for a small patient population to ensure it has been appropriately targeted. A similar approach could be successful for mepolizumab, with recipients potentially trialled for an initial 12 month period to ensure that the treatment has been effective at reducing exacerbations that require OCS use by around 50%.

We believe that a threshold of 4 or more exacerbations over the previous 12 months would be appropriate in further targeting the treatment to those most likely to benefit the most.

We disagree with the ERGs statement that defining the population without restricting the blood eosinophil count would have been a more appropriate way to define the severe eosinophilic asthma population. As the treatment is for severe eosinophilic asthma the blood eosinophil count is of primary importance. As highlighted, clinicians that we have consulted in preparing this response have stated that 150 cells/microlitre is within the normal range for most people and that therefore a count of 300 cells/microlitre would be more appropriate. Nevertheless, we acknowledge that the company did not choose to narrow the marketing authorisation in this respect.

Once again, we believe that the comparison of mepolizumab with omalizumab is inappropriate as they are primarily targeted at different subgroups of people with severe asthma “eosinophilic and allergic.

We are disappointed that the committees discussion throughout consideration of mepolizumab appears to have understated the reality for patients of sustained OCS use. While OCS may be effective for some people in helping to reduce exacerbations in their asthma, the intolerable consequences and detrimental impact to their quality of life and long-term health makes this a very difficult treatment for patients to tolerate. As one patient reflected to us, steroid treatment can take its toll on your body¦steroids change your personality and I become aggressive on them . Whilst this description is only used to identify an appropriate population it adds to the rhetoric that there is an effective existing treatment option for this group. The long-term side-effects of OCS highlights the need for new innovations that are clinically effective with improved quality of life.

As stated previously (3.3.31), we disagree with the appraisal committees preferred population used to assess mepolizumab, and in particular with the inclusion of severe asthma patients with a blood eosinophil count of 150 or more cells/microlitre. We do not believe that this represents an appropriate definition of the severe eosinophilic asthma population, and strongly recommend that NICE reconsiders and reassesses using a blood eosinophil count of 300 or more cells/microlitre." As mentioned previously (3.3.13) we believe that the St Georges Respiratory Questionnaire represents a more appropriate measure of quality of life than the EQ-5D.

To complement generic quality-of-life instruments and address issues specific to patients with asthma, researchers developed disease-specific quality-of-life questionnaires. Patient scores disease-specific questionnaires such as the St Georges Respiratory Questionnaire often correlate better with various physiologic measures and clinical indicators of asthma status than more generic instruments, with changes in these scores more sensitive to important but sometimes small changes experienced by patients with asthma (Ford et al 2003, http://www.ncbi.nlm.nih.gov/pubmed/12527612). The St George's Respiratory Questionnaire also used in COPD research, with one study comparing it to EQ-5D suggesting it demonstrated greater ability to discriminate among different levels of severity stages of the condition than generic measures of health, suggestive that it may provide studies with greater statistical power than EQ-5D to capture meaningful quality of life outcomes (Pickard et al 2011, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3096892/)

In addition, as highlighted in 3.3.28 the company mapped St George's Respiratory Questionnaire scores in the MENSA trial to EQ-5D using an algorithm based on a population with chronic obstructive pulmonary disease (not eosinophilic asthma). We believe that given the way this was mapped, it would have been more appropriate to have used the St George's Respiratory Questionnaire scores.

We are concerned that the scale of effects of regular OCS use has not been fully recognised in considering mepolizumab, as the potential to reduce OCS use would have a significant impact on those patients that experience the serious effects these can have. The side-effects are well-documented, including osteoporosis, psychological symptoms, Cushings syndrome, adrenal failure, diabetes, growth retardation, high blood pressure, cataracts and Addisons disease. The appraisal committee has recognised that the benefits related to avoiding the significant adverse effects of OCS use had not been fully captured in the QALY measure, and that accounting for this (along with the impact on carers) would reduce the ICER.

NB: GlaxoSmithKline is a member of Asthma UK's corporate membership scheme for FY 15/16, and within the last two years has contributed £47,500 in sponsorship for a project on Asthma Action Plans.

Comments on NICE Appraisal Consultation Document for the Single Technology Appraisal on Mepolizumab for treating severe refractory eosinophilic asthma [ID798]

British Association of Dermatologists
Therapy & Guidelines sub-committee

On behalf of the British Association of Dermatologists, thank you for the opportunity to comment on the Appraisal Consultation Document.

We note the following from the conclusions section (page 41):

> "The Committee agreed mepolizumab was innovative as its impact on the quality of life of carers, and the quality of life benefits of reducing oral corticosteroids were not captured in the model. The Committee agreed that accounting for this would reduce the ICER."

The adverse effects of corticosteroids have a significant cost to the patient, their carers and the NHS. It is essential this is considered in health economic modelling.

[redacted]
Therapy & Guidelines sub-committee

British Thoracic Society

It is stated that the DREAM study recruited patients on high dose oral steroids (it should be high dose ICS).

It is stated that the NICE guidance for Omalizumab stipulates that patients are eligible if they have 2 or more severe exacerbations per year, rather than 4.

This states that the ERG rejected using an exacerbation rate as part of the criteria as this can vary from year to year, however this has been used for Omalizumab. We feel an exacerbation criterion of 4 exacerbations per year as proposed by GlaxoSmithKline to be appropriate and more likely to represent a high risk population whilst still recognising the significant clinical benefit in both the MENSA and DREAM studies which recruited patients with 2 exacerbations in the previous year.

We suggest a more robust framework to assess treatment response to be more appropriate than that suggested by the company particularly in patients on maintenance oral corticosteroids.

The British Thoracic Society is grateful that NICE has decided to consider the use of Mepolizumab for treating severe refractory eosinophilic asthma. However we are disappointed that the outcome was not in favour of its use for this group of patients. Many patients could potentially benefit from this medication and it would represent a step change in the way clinicians would be able to manage their condition.

Severe asthma represents a spectrum of disease characterised by a number of different phenotypes. Recurrent asthma exacerbations are a major problem in some patients and can predominate in a subgroup with eosinophilic airway inflammation.

As such recent therapeutic developments have focused on a more individualised approach. Some patients are refractory to other asthma treatments and Mepolizumab represents an effective targeted therapy that in specific asthma patients may offer the relief they were hoping for.

Patients with severe asthma often have significant limitations to their quality of life, days of work lost and risk of death through exacerbations of their disease. Frequently the only options for treatment are significant amounts of inhaled medication and oral medications with potential adverse effects particularly with oral corticosteroids. Patients often describe that oral corticosteroids add a significant burden to their deterioration in quality of life and there are significant adverse effects to long term health including osteoporosis, infections, skin thinning, cataracts, weight gain, diabetes etc. that can add a significant burden to their quality of life often not captured in health related quality of life measures. It is increasingly recognised that the burden of treatment may be as important as the burden of disease in particular for patients requiring frequent courses of oral corticosteroids (OCS) or maintenance OCS.

Existing asthma-specific scales underestimate the overall burden of severe asthma and therefore underestimate the benefits of steroid sparing agents. This underestimation is important because the high cost of modern steroid-sparing agents requires accurate quality of life assessment to inform decision making (Hyland et al. Qual Life Res (2015) 24:631639).

Data from the Optimum Patient Care Research Database (OPCRD) and the BTS Difficult Asthma Registry shows that patients with severe asthma have substantial excess morbidity from multiple diseases and adverse effects associated with systemic corticosteroid exposure (Sweeney et al. Thorax 2016;71:339-346).

Those with multiple comorbidities are also most likely to be exposed to polypharmacy and it has been suggested by The King's Fund, Royal Pharmaceutical Society and NICE that guidelines be developed to take account of long term conditions that may coexist rather than a single-disease framework.

We urge the committee to reconsider their model and include the far ranging consequences of sparing the patient from the complications of oral corticosteroids and development of comorbidities that would require further healthcare utilisation, disutility and polypharmacy.

The only currently licenced monoclonal antibody for use in severe asthma is Omalizumab although specifically directed towards the allergic population. However, we do not feel the comparison of Mepolizumab with Omalizumab within the appraisal to be appropriate.

There are many patients with non-allergic severe asthma for whom Omalizumab is not suitable or who have failed to respond to Omalizumab and who have been waiting in anticipation for this class of drug. Mepolizumab has the potential to significantly reduce the considerable burden of disease in selected individuals through both reductions in exacerbations and oral corticosteroid burden. We feel there is no evidence to support a decision to exclude patients who have not responded to Omalizumab from being considered for Mepolizumab - this statement should be removed from the document.

The important comparison with Omalizumab is the judicious and responsible use of Omalizumab in the UK over the past 10 years which should provide assurance regarding appropriate future prescribing of high cost treatments in severe asthma.

We note that the economic models all make large assumptions - the NICE ERG cost per QALY is very different from Company's estimate.

The summaries for the patient groups described appear to be sound however we believe that in practice the most benefit to patients has been shown in those with high eosinophils and multiple exacerbations. Therefore a reassessment of the effectiveness in this particular group taking into account the significant effect of comorbidities avoided from reduced oral corticosteroid use would likely deliver a cost effectiveness Cost per QALY below the threshold required to recommend its use. We feel a review of the clinical and cost effectiveness in a more defined population (as proposed) would be more appropriate.

The expert opinion of the BTS severe asthma community is those patients with severe asthma with an eosinophilic phenotype (e.g. evidence of significant blood eosinophilia) and frequent exacerbations plus those with but requiring oral corticosteroids would be the most appropriate population to target.

Therefore, NICE may wish to consider a review of the proposed population incorporating the expert opinion of the BTS severe asthma network using a defined blood eosinophil count threshold for patients not on maintenance oral steroids.

Population definition:

- Adherent with treatment at step IV of the BTS/SIGN guidelines
- A blood eosinophil count of 500 or more cells/microlitre in the previous year
- 4 or more exacerbations in the previous year

Stopping criteria:

- Halving of exacerbation frequency after 12 months of treatment.

Patients maintained on oral corticosteroids

Population definition:

- Adherent with treatment at step V of the BTS/SIGN guidelines
- A blood eosinophil count of 150 or more cells/microlitre in the previous year

Stopping criteria:

- Halving of oral corticosteroids after 6 months of treatment.

The prescription of high cost therapies is already controlled within the NHS as is evidenced by the current arrangement for Omalizumab. The respiratory community that are like to prescribe Mepolizumab to the population described are currently developing an agreement where patients will need to be seen in a regional specialist clinic or discussed in a network of asthma specialists with agreed expertise prior to prescription. Patients will be expected to have been appropriately assessed, adherent with treatment, meet the diagnostic criteria for eligibility for prescription and be approved before prescribing treatment. Suitable monitoring should also be in place. Ref: (https://www.england.nhs.uk/wp-content/uploads/2013/06/a14-respiratory-sev-asthma.pdf).

This would ensure that prescribing practices are sound and eligibility procedures are robust for this potentially high cost intervention. As prescribing of any novel biologic agents will be through a severe asthma specialist network this should provide reassurance that only appropriate patients who have undergone a thorough systematic evaluation within a specialist severe asthma network would be considered. The respiratory community has considered the infrastructure required to deliver this treatment effectively and economically in detail.

Many of the members of the severe asthma group have been involved with patients who have received Mepolizumab and have seen significant benefit in these patients.
œAt Southampton we had quite a few patients enrolled in the trials for Mepolizumab - it was massively beneficial to them and we could see a real difference when they came back to clinic.

Plymouth Hospitals NHS Trust has been involved in three Mepolizumab clinical trials (15 patients) and we can attest that for some patients the effects have been utterly life changing.

Patient quote: ‘For the first time in my life I don’t feel like I have asthma’. Previously a poorly controlled oral steroid dependent severe asthmatic who now has complete asthma control at BTS step 3 and back to full time employment.

In summary BTS does not support restricting treatment to patients already on step 5 (i.e. regular OCS) as it would be detrimental to wait until patients develop the long term side effects of oral corticosteroid therapy.

We request that NICE review the clinical and cost effectiveness in a targeted population most likely to gain benefit as suggested above.

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Mr M Boysen
Programme Director, Centre for Health Technology Evaluation
National Institute for Health and Care Excellence
Level 1A, City Tower, Piccadilly Plaza
Manchester
M1 4BT

22nd April 2016

Dear Mr Boysen,

NICE Single Technology Appraisal (STA), Asthma (eosinophilic, severe) - mepolizumab [ID798] - Appraisal consultation document (ACD).

Thank you for your letter dated 29th March 2016 inviting comments on the above Appraisal Consultation Document (ACD), in which omalizumab (manufactured by Novartis) is mentioned.

The following document answers the questions below as requested by NICE:

If you require clarification on any aspects of our response, please do not hesitate to contact me.

Yours sincerely,

[redacted]

1. **Has all of the relevant evidence been taken into account?**

Novartis considers that the relevant evidence has generally been taken into account by the Appraisal Committee in preparing the provisional recommendations detailed in the ACD. However, we would like to comment on the administration and monitoring cost assumptions that have been used.

Administration cost assumption

Novartis believes mepolizumab may incur higher administration costs than omalizumab due to mepolizumab being available in a lyophilized powder formulation which requires reconstitution prior to administration compared to omalizumab being available as a pre-filled syringe formulation (PFS) that requires no preparation prior to administration. In September 2011, the PFS formulation for omalizumab replaced the previous lyophilised powder formulation and in the previous omalizumab MTA (TA278), based on UK nurse clinical expert opinion, this reduced omalizumab administration time from approximately 30 minutes to 10 minutes.

Monitoring cost assumption

GSK has assumed that mepolizumab will require less monitoring time than omalizumab. However, Novartis believes that based on feedback from UK Healthcare Professionals the post-dose monitoring for mepolizumab and omalizumab will follow the same protocol in clinical practice.

2. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

Novartis considers the summaries of clinical and cost-effectiveness in the ACD to be, on the whole, reasonable interpretations of the evidence. However, there are some inaccuracies that are summarised below:

Omalizumab NICE Guidance criteria

The NICE criteria for omalizumab treatment in severe allergic asthma are not accurately reflected in the ACD document and should be corrected (ACD, section 3.17 and 3.18). The document states that the NICE Guidance for omalizumab stipulates that patients should have had two or more exacerbations needing treatment with systemic corticosteroids in the previous year to receive omalizumab. However, the NICE guidance for omalizumab (TA278) states in section 1.1 that eligible patients are those ‘who need continuous or frequent oral steroids (defined as 4 or more courses in the previous year)’.

Indirect comparison between omalizumab and mepolizumab

Regarding the above indirect comparison, Novartis is in agreement with the Appraisal Committee regarding the results being highly uncertain for decision making (ACD, section 4.9). The size of the overlapping population is small and there is significant heterogeneity

between the patient populations studied, specifically with regard to the severity of disease for the different trial populations. The population receiving mepolizumab was more severe than for those receiving omalizumab and therefore the populations are not comparable. Given that treatment effects may be more pronounced in a more severe population, it is likely the meta-analyses carried out by GSK may have under-estimated the treatment effects associated with omalizumab. Additionally, there are also significant differences in the trial designs, inclusion criteria, endpoints and definitions of endpoints between the studies.

Description of an omalizumab study

The description of the EXTRA study in the ACD document is incorrect, this study enrolled severe asthma patients not moderate to severe patients as stated (ACD, section 3.18).

GSK proposed patient populations

Regarding eosinophil cut-off levels (ACD, section 3.34), we agree that an eosinophil threshold of 150 mg/ml is a relatively low count in the normal range.

Size of the overlapping population for omalizumab and mepolizumab

Novartis is in agreement that the size of the overlapping population is very small (ACD, section 4.9).

Committee's preferred population

The term 'dependency on maintenance oral corticosteroids' (ACD, section 4.6) may be ambiguous in clinical practice and therefore we suggest that 'dependency on continuous oral corticosteroids' is a clearer description of the population.

3. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

Based on the evidence considered, Novartis agrees that a comparison with omalizumab is not feasible (see comments in section 2 above).

4. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

Novartis has no comments.

5. Response to the manufacturers economic model

The version of the model received was not executable due to the extent of the password protection. This restricted the scope of our review to structural settings and input values only, on which we have no comments beyond those already outlined in this response.

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Professor A J Wardlaw FRCP PhD
Professor of Allergy and Respiratory Medicine and Director of the Leicester Institute for Lung Health and the NIHR Leicester Respiratory BRU

21.04.2016
Jeremy Powell
NICE Appraisal for Mepolizumab

Dear Jeremy

Re: Response to NICE appraisal for mepolizumab

I am broadly in agreement with the comments made in the appraisal document. However critically the criteria that are proposed for the target population by the committee as set out in 4.6 are not appropriate. These criteria would exclude many people who would benefit from the drug and would lead to considerable gaming of the system where physicians would treat people with maintenance oral corticosteroids just so they fit the criteria. Asthmatics with eosinophilic asthma who were well controlled on oral steroids with normal eosinophil counts and no exacerbations would miss out on the opportunity of being able to reduce or even stop their oral steroids. This drug will benefit people who 1) have eosinophilic asthma 2) are not well controlled unless they are on systemic corticosteroids. After discussion with colleagues I would therefore propose the following criteria to define the preferred population.

1) Evidence of eosinophilic asthma based on an eosinophil count greater than or equal to 300/ul within the last five years, (eosinophilic asthma is a stable phenotype).
2) Evidence of uncontrolled disease despite objective evidence of adherence to high dose inhaled corticosteroids. Uncontrolled disease is defined as either:
   a) ≥ 3 severe exacerbations in the previous 12 months (defined as a need for high dose oral steroids for more than 3 days),
   b) Dependency on continuous daily oral steroids (equal or greater than 7.5mg/day for at least six months).

Mepolizumab should only be given after the patient has been assessed in a specialist asthma centre as recognised by NHS England and treatment recommended by the centre after discussion in a multi-discplinary team meeting.

I would also once again make the point that mepolizumab is without doubt an important step forward in our efforts to improve the quality of life and reduce the risk of life threatening events in people with severe asthma and I think it is essential that it is made available to the asthma community.

I hope these comments are helpful.

Kind regards

Andy Wardlaw

Comments on the ACD Received from the Public through the NICE Website

Organisation	**BTS Severe asthma network**
Role	Consultant Respiratory Physician
Conflict	Along with many of my co-authors I have participated in phase III studies with mepolizumab

Response by the BTS severe asthma network to the appraisal consultation document Mepolizumab for treating severe refractory eosinophilic asthma

Introduction

As clinicians looking after patients with severe asthma in the UK, we would like to comment on the NICE appraisal consultation document on mepolizumab for treating severe refractory eosinophilic asthma. We are well aware of the huge morbidity associated with severe asthma and the very significant side effects of oral corticosteroids, the only viable treatment option for most of these patients.

We strongly disagree with the draft recommendation that mepolizumab is not recommended as an add-on for treating severe refractory eosinophilic asthma. After careful review we feel that the appraisal committee did not identify the correct patient population and has misinterpreted the underlying pathophysiology of this disease process. In addition some of the modeling assumptions made by both the company and the ERG are open to question. The current provisional recommendations are not sound and are not a suitable basis for guidance to the NHS.

Clinical effectiveness

We note the proposed population of adults with a blood eosinophil count of 150 cells/microlitre or more at the start of treatment (regardless of their value in the year before screening); and 4 or more exacerbations in the previous year, or dependency on systemic corticosteroids; the restricted population, which is as the proposed, but excludes patients on systemic OCS; and finally population 3, which was requested by the ERG of adults with a blood eosinophil count of 150 cells/microlitre or more at the start of treatment, and fewer than 4 exacerbations in the previous year, and dependency on systemic corticosteroids.

With regards the company's clinical effectiveness submission, statements 3.17 and 3.18 are incorrect as the 2013 NICE HTA for omalizumab for treating severe persistent allergic asthma stipulates 4 or more exacerbations in the past 12 months (rather than the stated 2).

Cost effectiveness

We do not agree with the mean age of 50.1 years provided in the model (3.23). The most recent published data from the BTS severe asthma registry suggests a median age of 46 at initial presentation to a severe asthma service (interquartile range of 34-55), but an age at initial diagnosis of 16 (4-33) (Gibeon et al Chest 2015; 148: 870-6). We agree that the criteria for stopping treatment must be more robust than the company's suggestion that patients should continue on treatment if there is no increase in exacerbations after 12 months (3.24). Measuring the effect on exacerbation frequency versus oral corticosteroid sparing will require different time periods to assess response and our proposed stopping rules are discussed later within this document.

ERG comments
We agree with the ERG that the rate of exacerbation chosen by the company for patients who continue mepolizumab could be inappropriate and that it is logical to analyse data from the COSMOS study, which measured rates of exacerbation for a full year, as this would account for the seasonal nature of asthma exacerbations (3.41).

We agree with the ERG that using the average duration of the exacerbations in MENSA, instead of the duration of exacerbations based on the Lloyd et al. study, would have been more appropriate (3.43).

However, we are very surprised that the ERG felt that the company should have used the mortality rate from Roberts et al, Respir Med 2013; 1172-7 (3.44). Clearly this paper does not include fatal asthma attacks that do not occur within 30 days of an admission to hospital when asthma was coded on the discharge summary. The recent RCP National Review of Asthma Deaths clearly demonstrates that many people suffer from a fatal asthma attack at other time points and the increased mortality associated with increasing age reported in the Roberts study may well be explained by confounding co-morbidities or inappropriate labeling of patients with COPD as suffering from asthma. Roberts et al is not representative of all asthma deaths and there is a high likelihood of confounding and it is therefore inappropriate for this analysis.

(3.46) It is not clear that the ERG used the most up to date research when investigating the impact on the ICER of reducing oral corticosteroid use (Sweeney et al Thorax. 2016 Apr;71(4):339-46. doi: 10.1136/thoraxjnl-2015-207630. Epub 2016 Jan 27)?

The ERG are incorrect in their assumption that defining a population based on exacerbations rather than eosinophil count would have been more appropriate (3.47). The rationale for this statement is provided later in the document.

We note the ERG analysis for the proposed and restricted populations (Table 5) and consider them flawed as they include modeling the Roberts data and using EQ-5D, which is not validated in severe asthma and does not take into account one of the main benefits of mepolizumab, which is oral corticosteroid sparing.

Committee discussion
We consider that severe refractory asthma is included within the ERS/ATS definition for severe asthma (Chung et al Eur Respir J 2014; 43: 343-73). This clearly states that patients at GINA steps IV and V (broadly applicable to BTS/SIGN steps) can have severe or therapy resistant asthma. We routinely identify these patients in our clinical practice via a systematic assessment protocol and review by relevant members of the multidisciplinary team.

Eosinophilic asthma is associated with elevated blood and/or sputum eosinophils, which will vary both over time and in response to treatment. Biopsy specimens from nasal polyps and rapid response to OCS (4.3) are not used to make the diagnosis of eosinophilic asthma.

We disagree with the committee's decision to arbitrarily create a de novo severe asthma population for the appraisal as explained in the following paragraphs.

Blood eosinophils have been demonstrated to predict response to a variety of biological agents targeting T2 high inflammation including mepolizumab, omalizumab and benralizumab. It is clinically plausible that the higher the blood eosinophil count, the more likely that a patient will respond to a targeted eosinophilic therapy. When considering what is the normal range for blood eosinophils it is critically important to take medication into account. Whilst a blood eosinophil count of 150 cells/microlitre is undoubtedly in the normal range for a member of the general population, the same count would suggest refractory eosinophilic disease in a patient with severe asthma taking 20mg of prednisolone per day.

The company's proposed eosinophil cut off level of 150 is based on analysis of multiple factors present at baseline in the DREAM study including markers of eosinophilic inflammation (blood and sputum eosinophils and exhaled nitric oxide) and baseline covariates. We agree that a threshold of 150 cells/microlitre is not intuitively elevated in patients taking inhaled corticosteroids. However, the data provided by the company suggests a clear increased reduction in exacerbation risk in patients with a blood eosinophil level of 500 cells/microlitre or higher when compared with lower blood eosinophil levels.

We think that the committee were wrong to decrease the number of exacerbations in the target population to 2 or more per year. Clearly we would want to offer this novel and efficacious therapy to all patients with severe eosinophilic asthma at risk of future exacerbations, but we understand that this would not be cost effective and feel that a total of 4 or more exacerbations per year helps define a high cost and high future risk population.

With regards statement 4.6 continuous oral corticosteroids should be seen as the last resort due to the very significant morbidity associated with their long term use (Sweeney et al, 2015). Maintenance corticosteroids are not always effective for patients with severe asthma and patients frequently exhibit at least partial steroid resistance and often remain at risk of future asthma exacerbations.

We disagree that the SIRIUS trial may be more generalisable to clinical practice than MENSA and DREAM (4.8). Continuous oral corticosteroids are frequently the last resort given their significant side effect profile and the most common driver to initiate continuous oral corticosteroid usage is frequent exacerbations. The overall aim of mepolizumab is to decrease both exacerbation frequency and steroid burden, which are intrinsically linked together.

Statement 4.10 is completely illogical, whilst it is possible to determine that an individual patient is suffering from T2 high inflammation, it is impossible to determine whether that is being driven by allergy (IgE), IL-5, IL-4/13, TSLP, IL-25, IL-33 or any combination of these cytokines. There is no clinical or immunological basis to say that a patient who has failed a trial of omalizumab will not respond to mepolizumab and we recommend that this statement is removed from the document as it would be wrong to discriminate against patients that have failed a trial of omalizumab.
The opinion of the committee that people whose disease had responded to mepolizumab were likely to have less severe disease than whose disease had not responded (4.14) is not based on fact. Severe asthma is heterogeneous even within the eosinophilic subtype and response to an anti-IL-5 monoclonal antibody simply confirms that IL-5 plays a key role in eosinophil biology in that individual, but has no connection with severity measured in terms of treatment burden and exacerbation frequency.

There was a clinically and statistically significant improvement in SGRQ in the

MENSA study, which contradicts the view from the clinical experts that mepolizumab was unlikely to have an effect on symptoms (4.18).

Given the above we do not think that the preferred subpopulation in 4.21 is either clinically or scientifically relevant. Clearly if the wrong population is identified it is not surprising that the ICER generated is £72,500 per QALY gained.
We therefore feel that the committee has misinterpreted both the available clinical data and expert opinion to determine the incorrect patient population for mepolizumab. In our opinion as both clinical and research experts in the field the population should be split into recurrent exacerbators and patients maintained on oral corticosteroids with different entry criteria and stopping rules associated with each population. This is key as there is a significant difference in the expected level of blood eosinophils between these 2 patient populations and the outcomes that predict response are also different and will require measurement over different time periods.
Recurrent exacerbators

Population definition:
- Adherent with treatment at step IV of the BTS/SIGN guidelines
- A blood eosinophil count of 500 or more cells/microlitre in the previous year
- 4 or more exacerbations in the previous year

Stopping criteria:
- Halving of exacerbation frequency after 12 months of treatment.

Patients maintained on oral corticosteroids
Population definition:
- Adherent with treatment at step V of the BTS/SIGN guidelines
- A blood eosinophil count of 150 or more cells/microlitre in the previous year

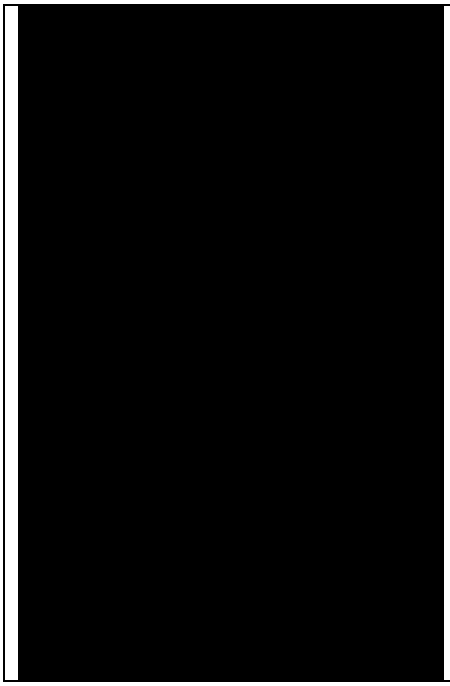
Stopping criteria:
- Halving of oral corticosteroids after 6 months of treatment.

Conclusion

We have shown that as a community we use new high cost therapies economically and effectively. The total omalizumab prescriptions in the UK are a small fraction of those in other developed countries. We are confident that we would do the same with mepolizumab, particularly as precision, biomarker directed management is possible with this agent.

We have already discussed and agreed assessment protocols and plans for administering the treatment in a controlled and centralised way through the network of NHS England commissioned severe asthma centres and would encourage the committee to reflect this in the final guidance. We are confident that this treatment will be used effectively and economically, and, most importantly, in the patients who have the most to gain from treatment if mepolizumab is prescribed for the populations that we have suggested.

The following consultant respiratory physicians have been involved in producing this document and endorse its findings:



Organisation	**North West Severe Asthma Service, representing 8 million population in NW England**
Role	Senior Lecturer & Consultant Respiratory Medicine
Conflict	None declared

North West Severe Asthma Service, response to NICE Mepolizumab appraisal.

The North West Severe Asthma Service (NWSAS) provides a commissioned service to severe asthma sufferers from across the North West of England to a catchment population of between 5 and 8 million. It collaborates with neighbouring regions including North Wales and captures referrals from a wider population. Decisions on funding of existing but expensive therapies such as omalizumab and bronchial thermoplasty are made by an MDT committee of eight hospital specialist teams.

In this response we represent the patients with severe asthma and the Health Care providers to these patients in our views. Severe asthma patients suffer a huge burden of therapy, cost (personal and national), risk (severe exacerbations including life-threatening or -ending events) and reduction in quality of life.

In some of these cases, the impacts could be ameliorated or resolved by appropriate adherence by patients to standard available therapy, as such all patients being considered for expensive treatment modalities should have detailed adherence checks. In others, the disease thwarts the impact of all standard therapies and continues to cause severe disease and life threatening exacerbations.

The true cost to the nation of severe asthma is unknown, in part as the costs of long term side effects of existing therapies, most notably maintenance oral corticosteroids (OCS) are underestimated. The impacts from individuals unable to work due to chronic illness from an early age, from frequent time off sick, or time lost due to side effects of current therapies (OCS) are effectively unknown.

This document has been written and approved by the Network and represents the

views of all members of the Service

NICE provisional response

NWSAS were disappointed with both the GSK application document and the decision of the panel to reject the submission and potentially reject the use of mepolizumab.

Patients with severe asthma (including those who are not suitable for omalizumab) and who have an eosinophilic phenotype, represent a huge unmet need and these patients are reliant on frequent rescue, or maintenance oral steroids despite adequate use of standard maintenance therapy.

The genuine cost of long term oral corticosteroid use to the nation is unknown. Patients suffer neuro-psychiatric adverse events, obesity, sleep apnoea syndrome, diabetes, osteoporosis, glaucoma, hypertension, cataracts and avascular necrosis. Most patients who rely on maintenance or frequent use of oral steroids are unable to work and require disability payments and fail to contribute income tax and additional financial contributions to the state. NICE have failed to attempt to calculate these costs or accept them in their calculation of the impact of severe asthma and its impact on the health of the nation and the failure to do so is a derogation of responsibility in terms of the cost benefit ratio of novel therapies including mepolizumab. As asthma effects a working age population, this is critically important when comparing the impact of disease to older age populations (such as COPD for example) in cost effectiveness models.

GSK application

NWSAS were disappointed that there was a total failure of GSK to accept the UK consensus view, that a threshold of 0.15 for blood eosinophils does not represent a genuine eosinophilic phenotype of asthma. We are confident NICE will see this view represented in multiple responses. Using sputum eosinophilia as the gold standard, data has been published indicating that at a threshold of 0.15 within a clinical severe asthma population identifies a large sub-group within whom only 50% are genuinely eosinophilic phenotype when confirmed by sputum eosinophil measurement. Using a higher threshold would improve specificity for those patients in need of mepolizumab. A more realistic threshold should have been submitted.

GSK also appeared to suggest that mepolizumab would be a better option than omalizumab. Experience of the latter drug in clinical practice goes back nearly ten years. GSK calculation suggests a superiority of Mepolizumab over omalizumab. The calculation by NICE favours omalizumab. Either way the preferential impact is marginal. The appropriate clinician response should be to use the existing therapy which has a known safety profile and is widely trusted for its impact in clinical practice. It would be irrational to introduce new drugs for patients suitable for existing therapies, even if there was a marginal positive benefit of the novel treatment, until real life data and experience was gained.

GSK failed to acknowledge or deal with issues surrounding adherence to therapy and the need to objectively assess this confounding factor before considering introducing novel therapies, or that such assessment is now standard of care within severe asthma commissioned services.

GSK failed to consider the assessment of failure to respond to mepolizumab and

whilst formal data from trials fails to identify a proven mechanism of identifying true therapy response or lack of it, no attempt is used to acknowledge or identify those patients who genuinely do not respond in any way whether pragmatic or scientifically based such a suggestion would be.

NICE response

It is unclear if the NICE committee completely understood the implication of clinical phenotyping of asthma. The newly commissioned severe asthma services, around the UK, perform systematic evaluation of all referred patients and act with a nationally concordant approach. First assessments of severe asthma patients involve looking for specific clinical features, including allergic phenotype (including those suitable for omalizumab, which represents approximately 15% of the total severe asthma population), those with eosinophilia with or without allergy, including those with allergy who are unsuitable for omalizumab.

There is no real appreciation of the depth of assessment of adherence to standard therapy in current severe asthma services. Novel data from NWSAS documents that 15-20% of patients previously considered suitable for omalizumab are now deemed unsuitable on the basis of lack of adherence to standard therapy when data is reviewed at the regional MDT before treatment trials can be approved. The same mechanism would apply to patients being considered for mepolizumab in the NWSAS region and hopefully nationally who undergo the same screening and assessment processes.

There is no acceptance that currently available commissioned services have accurately, professionally and rationally assessed patients suitable for omalizumab. Data from real life clinical practice have shown an improvement in terms of response rate to therapy from approximately 63% up to 80 and 83% in these sequential real life clinical studies. The expected treated patient population remains substantially below the numbers expected from NICE's own data at the onset of NICE appraisal.

NICE continues to dismiss data on the cost of OCS use as a maintenance therapy or as a frequent high dose intermittent treatment. It is currently estimated that lost productivity or time off work from asthma alone costs the nation nearly a billion pounds per annum, the majority of this from patients with more severe phenotypes. The cost to the nation is underestimated as NICE fails to consider the national benefit of returning working age patients back to part time or full time work by improving asthma control or the reduction of time off on sick leave for those patients in current employment with severe asthma. Returning a small proportion of patients to full time work would dramatically impact on the REAL cost to the nation.

Potential benefits of mepolizumab

Mepolizumab used in the appropriate population would:

- Improve quality of life for patients with an unmet need
- Reduce costly exacerbations, which are in extreme cases fatal
- Reduce reliance on oral corticosteroids
- Reduce long-term side effects and costs of OCS use in patients with severe eosinophilic asthma.
- Return patients on long-term sickness to part-time or full time work
- Reduce real costs to the nation of long-term chronic illness.

NWSAS recommendations

A more stringent restriction for patients suitable for mepolizumab should be applied than that introduced by GSK in their original application. This would reduce the QALY costs of mepolizumab and identify an appropriate and cost beneficial therapy to patients and the nation

Eosinophilic phenotype should be determined by a combination of proven adherence and eosinophilia despite regular or frequent courses of OCS in patients who have undergone systematic evaluation.

As such we believe

Mepolizumab should only be considered and introduced by commissioned severe asthma centres participating in MDT, multi-centre network meetings

For STEP 4 patients.

Eosinophilic phenotype should be confirmed by the presence of blood eosinophilia at a threshold of at least 0.5 within the last 12 months in patients at step 4 of the BTS therapy guidelines who have required four or more bursts of oral steroids in the preceding year. Additionally, such patients would be required to demonstrate adherence to therapy, with greater than 66% collection of their usual prescribed inhaled corticosteroid (ICS) treatment demonstrated from primary care prescription records.

For STEP 5 patients.

Eosinophilic phenotype should be confirmed in patients with a threshold of at least 0.5 in the time going back to 12 months prior to commencing long term systemic corticosteroids

OR

If such criteria regarding pre-systemic corticosteroid blood eosinophil levels are not met, then a threshold of at least 0.3 should be applied for the preceding 12 months (on systemic corticosteroids) as long as patients are proven adherent (as determined by measurable serum prednisolone levels, and a suppressed random serum cortisol). The rationale for this differential threshold is the reduced likelihood of a higher eosinophil level in those patients taking maintenance OCS

Patients suitable for omalizumab, should be trialled with this therapy first. If they are proven non-responders and still satisfy the above criteria, they should be considered for a trail of mepolizumab.

Response to mepolizumab should be determined by a greater than 50% reduction in exacerbations, OR a 50% reduction in maintenance steroid dose, OR a combination of the above that results in a 50% reduction of total OCS dose (grams per year) in the 12 months post therapy, compared to 12 months pre therapy, as determined objectively from prescribing records. Those deemed to be non-responsive should have therapy removed at 12 months at the latest.

We give three real life examples below to use as examples of how these thresholds would be applied

Patient Examples

- MW (male 35) was eosinophilic whilst prescribed high dose ICS, he had five OCS-requiring exacerbations in the last 12 months as proven by GP prescribing records. Total IgE was over 2,000 kU making him unsuitable for omalizumab. Prescribing records of ICS were obtained in preparation for discussion at the NWSAS

MDT. MW had only collected four canisters of ICS over an 18 month period and therefore was deemed unsuitable for treatment with biologics due to non-adherence.

- NS (female 28) is eosinophilic with a blood eosinophil of 0.87 despite maintenance OCS at 40mg per day, detectable prednisolone levels and a totally suppressed cortisol level. In 2013 when she had a IgE of 350 kU with house dust mite RAST positivity, she had a 16 week omalizumab trial. She failed to respond in terms of AQLQ and ACQ. She had a bronchoscopy to assess suitability for bronchial thermoplasty and had a severe asthma exacerbation post bronchoscopy, and hence bronchial thermoplasty could not be considered. NS would therefore fulfil the NWSAS proposed treatment criteria for a trial of mepolizumab. A successful treatment trial would be defined by a reduction on her maintenance prednisolone dose to 20mg per day or lower at the 12-month assessment visit.

- JA had a blood eosinophil count of 0.65 three years ago and then was prescribed maintenance oral prednisolone at 15mg per day. JA was subsequently adherent to OCS therapy as determined by random serum prednisolone level and reduced cortisol, and to ICS on basis of ICS prescription data. Annual hospitalisation and OCS requiring exacerbations dropped from 2 and 6 per annum respectively to 0 and 2 per annum respectively since initiating maintenance OCS. Despite adherence to OCS and ICS maintenance eosinophils remained between 0.3 and 0.4 for the last 12 months but did not exceed 0.5. JA is suitable for a trial of mepolizumab under our recommendations.

Summary

NWSAS hopes and believes that NICE will review their decision based on our and other health care and patient recommendations, further compromise from GSK and cost effective therapy for a much needed population can be provided in a rational and cost beneficial model.

Mepolizumab for treating severe eosinophilic asthma: A Single Technology Appraisal

ERG critique of company's response to the ACD

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	Date completed (09/02/2016)

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 15/06/06.

Executive Summary

New evidence was presented by the company and new results were presented for three analyses.

- Analysis 1: Patients on maintenance oral corticosteroids (mOCS) and ≥2 exacerbations in previous year; not limited by eosinophil count (though all trial patients had eosinophils ≥150/μL at screening and/or ≥300/μL in previous year)
- Analysis 2: Patients on mOCS and/or ≥4 exacerbations in previous year; not limited by eosinophil count (though all trial patients had eosinophils ≥150/μL at screening and/or ≥300/μL in previous year)
- Analysis 3: Patients on mOCS and/or ≥4 exacerbations in previous year; and blood eosinophils ≥300/μL in previous year

The first analysis was subdivided into the full intention to treat (ITT) population and also for the ITT population excluding those patients not on mOCS.

The base case ICERs presented by the company are provided in Table 1. In the scenario analyses conducted by the company within Analyses 2 and 3, the ICERs did not increase above £29,000.

The ERG conducted a base case analysis following the Committee's preferred assumptions with the company's revised model. The base case ICERs calculated by the ERG are considerably higher (see Table 1). The ERG notes that the main drivers of the ICER are:

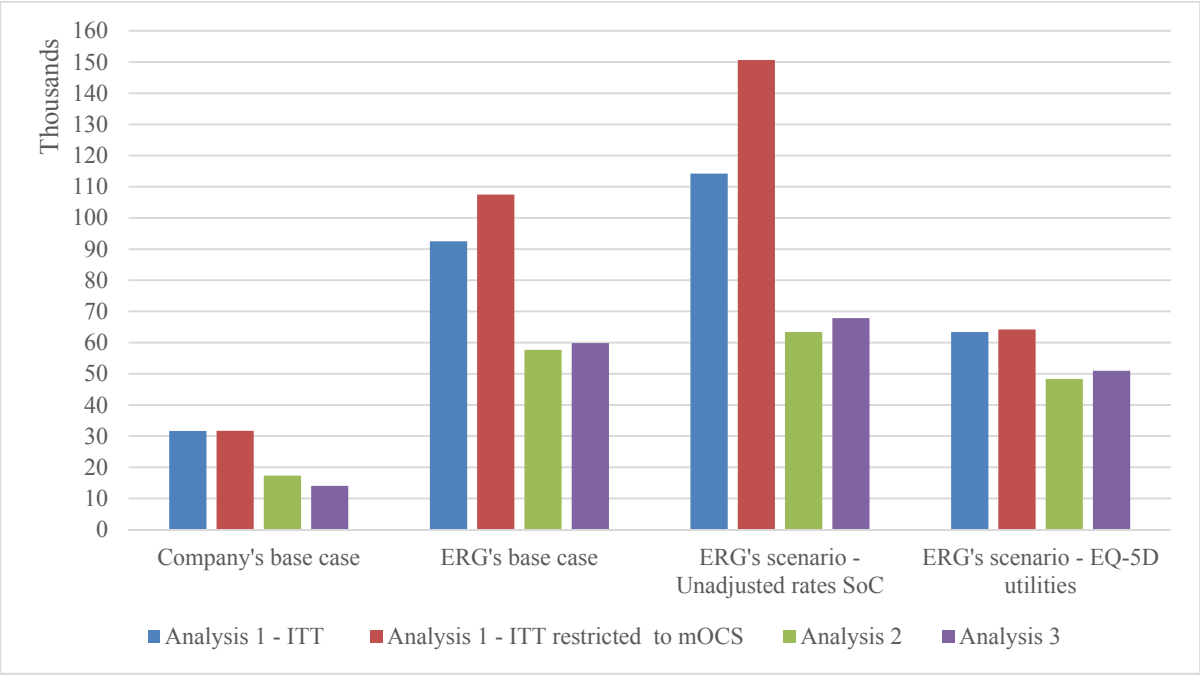
- Assuming that mepolizumab does not give a utility benefit over and above that associated with reduced exacerbations.
- Using the asthma mortality rates calculated combining Watson et al.[1] and Roberts et al.[2]
- Using the in-trial exacerbation rates from MENSA for patients on standard of care (SoC)

Table 1: Summarised base case ICERs (£/QALY) for mepolizumab vs. SoC

	Company base case	ERG base case analysis using Appraisal Committee preferred assumptions
Analysis 1: Full ITT	£31,659	£92,500
Analysis 1: ITT restricted to those on mOCS	£31,734	£107,499
Analysis 2	£22,305	£57,708
Analysis 3	£22,134	£59,859

Scenario analyses undertaken by the ERG indicated that the following assumptions produced a noticeable increase in the ICER: using SoC rates taken from MENSA without adjustment; assuming higher rates of attrition; and assuming waning of treatment over time. Using the EQ-5D data observed in DREAM noticeably reduced the ICERs but for no scenario did the ICER fall below £45,000 per QALY. Figure 1 shows a summary of the ICERs reported by the company along with those calculated by the ERG for its base case and scenario analyses.

Figure 1: Base case and scenario ICERs (£/QALY) for mepolizumab vs. SoC from the analyses undertaken by the company and the ERG



Introduction

Following the publication of the Appraisal Consultation Document (ACD) the company has provided, in agreement with NICE, clinical and cost effectiveness evidence related to a revised proposed population, namely patients who:

- ***have been diagnosed with severe refractory eosinophilic asthma,***
- ***and need continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)***
- ***and have a blood eosinophil count of ≥300 cells/μL in the last year'***

The company further restricted this population to those with blood eosinophils ≥300/μL in previous year.

In addition, the company present an analysis using the appraisal committee's preferred population that was

- not limited by blood eosinophil count,
- at least 2 exacerbations in the previous year, and
- limited to refractory patients having maintenance corticosteroids.

Summary of new populations in company response to ACD

The company provides data and analyses for three populations, summarised below:

- Analysis 1: Patients on mOCS and ≥2 exacerbations in previous year; not limited by eosinophil count (though all trial patients had eosinophils ≥150/μL at screening and/or ≥300/μL in previous year)
- Analysis 2: Patients on mOCS and/or ≥4 exacerbations in previous year; not limited by eosinophil count (though all trial patients had eosinophils ≥150/μL at screening and/or ≥300/μL in previous year)
- Analysis 3: Patients on mOCS and/or ≥4 exacerbations in previous year; and blood eosinophils ≥300/μL in previous year

The ERG's critique of the company's response to the ACD has been subdivided into five broad categories: an executive summary providing key results, parameters to which the ICER is particular sensitive and conclusions; an evaluation of the clinical evidence presented by the company; key issues, matching those presented within section 1.6.1 of the company's response; reproduction of the results presented within the company's response to the ACD; and the results generated by the ERG using different sets of assumptions to those used by the company.

An evaluation of the key clinical evidence presented by the company

A summary of clinical results presented in the company's response to the ACD is provided in Table 2 and Table 3. Discussion points relating to pertinent issues raised within the company's response to the ACD follow these tables.

Table 2: Rate ratios for clinically significant exacerbations for mepolizumab compared with placebo

	Rate ratios (95% CI)					
	Modified ITT population	**Proposed population**	**Proposed restricted population**	**Analysis 1 in company ACD response**	**Analysis 2 in company ACD response**	**Analysis 3 in company ACD response**
	• **Eos ≥150 or ≥300** • **≥2 exac**	• **Eos ≥150** • **≥4 exac or mOCS**	• **Eos ≥150** • **≥4 exac**	• **ITT restricted to mOCS**	• **≥4 exac or mOCS**	• **Eos ≥300** • **≥4 exac or mOCS**
MENSA (75mg IV)	0.53 (0.39 to 0.71)	0.40 (0.24 to 0.67)	0.39 (0.22 to 0.68)	Not reported	0.44 (0.29 to 0.67)	0.47 (0.30 to 0.73)
MENSA (100mg SC)	0.47 (0.35 to 0.63)	0.50 (0.32 to 0.78)	0.39 (0.23 to 0.67)	Not reported	0.54 (0.37 to 0.79)	0.56 (0.37 to 0.85)
MENSA pooled (75mg IV and 100mg SC	0.50 (0.39 to 0.64)	Not reported	Not reported	Not reported	Not reported	Not reported
DREAM (75mg IV)	0.52 (0.39 to 0.69)	0.36 (0.24 to 0.55)	0.31 (0.18 to 0.53)	Not reported	0.43 (0.29 to 0.63)	0.42 (0.27 to 0.64)
SIRIUS (100mg SC)	0.68 (0.47 to 0.99; p value 0.042)	0.77 (0.51 to 1.17; p value 0.222)	0.81 (0.40 to 1.64; p value 0.556)	Not reported	0.68 (0.47 to 0.99; p value 0.042)	0.60 (0.40 to 0.90; p value 0.014)
DREAM + MENSA (75mg IV and 100mg SC)	0.51 (0.42 to 0.62)	0.41 (0.31 to 0.55)	0.35 (0.25 to 0.50)	Not reported	0.47 (0.36 to 0.60)	0.47 (0.36 to 0.62)
DREAM + MENSA + SIRIUS (75mg IV and 100mg SC)	Not possible	0.50 (0.40 to 0.64)	0.42 (0.30 to 0.57)	Not reported	0.52 (0.43 to 0.65)	0.51 (0.01 to 0.64)

Abbreviations: ACD, Appraisal Consultation Document; CI, confidence interval; ITT, intention to treat; IV, intravenous; SC; subcutaneous.

Table 3: Rate ratios for exacerbations requiring hospitalisation for mepolizumab compared with placebo

	Rate ratios (95% CI)					
	Modified ITT population	**Proposed population**	**Proposed restricted population**	**Analysis 1 in ACD response**	**Analysis 2 in ACD response**	**Analysis 3 in ACD response**
	• **Eos ≥150 or ≥300** • **≥2 exac**	• **Eos ≥150** • **≥4 exac or mOCS**	• **Eos ≥150** • **≥4 exac**	• **ITT restricted to mOCS**	• **≥4 exac or mOCS**	• **Eos ≥300** • **≥4 exac or mOCS**
MENSA (75mg IV)	0.61 (0.23 to 1.66)	0.28 (0.05 to 1.45)	0.19 (0.03 to 1.31)	Not reported	0.14 (0.03 to 0.66)	0.16 (0.03 to 0.89)
MENSA (100mg SC)	0.31 (0.11 to 0.91)	0.55 (0.15 to 2.03)	0.49 (0.11 to 2.11)	Not reported	0.28 (0.08 to 0.99)	0.29 (0.07 to 1.23)
MENSA pooled (75mg IV and 100mg SC	0.44 (0.19 to 1.02)	Not reported	Not reported	Not reported	Not reported	Not reported
DREAM (75mg IV)	0.61 (0.28 to 1.33)	0.45 (0.14 to 1.43)	0.50 (0.13 to 1.97)	Not reported	0.42 (0.16 to 1.11)	0.69 (0.22 to 2.21)
SIRIUS (100mg SC)	Not possible	Not possible	Not possible	Not possible	Not possible	Not possible
DREAM + MENSA (75mg IV and 100mg SC)	0.50 (0.28 to 0.89)	0.44 (0.19 to 1.02)	0.43 (0.16 to 1.12)	Not reported	0.32 (0.15 to 0.68)	0.44 (0.18 to 1.05)
DREAM + MENSA + SIRIUS (75mg IV and 100mg SC)	Not possible	Not possible	Not possible	Not possible	Not possible	Not possible

Abbreviations: ACD, Appraisal Consultation Document; CI, confidence interval; ITT, intention to treat; IV, intravenous; SC; subcutaneous.

The relationship between blood eosinophils at screening and exacerbations

The company states that there is a greater reduction in exacerbations with mepolizumab for patients with higher eosinophil levels at screening. Data for this are reproduced in Figure 2 for DREAM and Figure 3 for MENSA. The ERG concludes from these data that while it could be argued that there is a greater reduction in exacerbations as eosinophils increase, this most prominent only for the >500 cells/μL (>50 GI/L) subgroup.

Figure 2: **Rate of Clinically Significant Exacerbations by Baseline Blood Eosinophils (DREAM, ITT Population, all IV doses) reproduced from CS Figure 12**

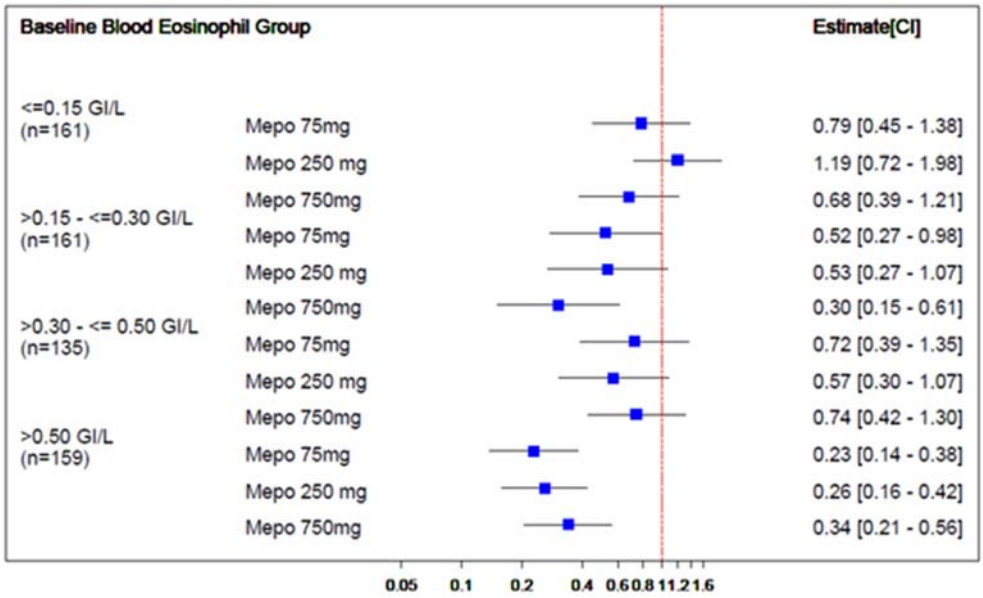
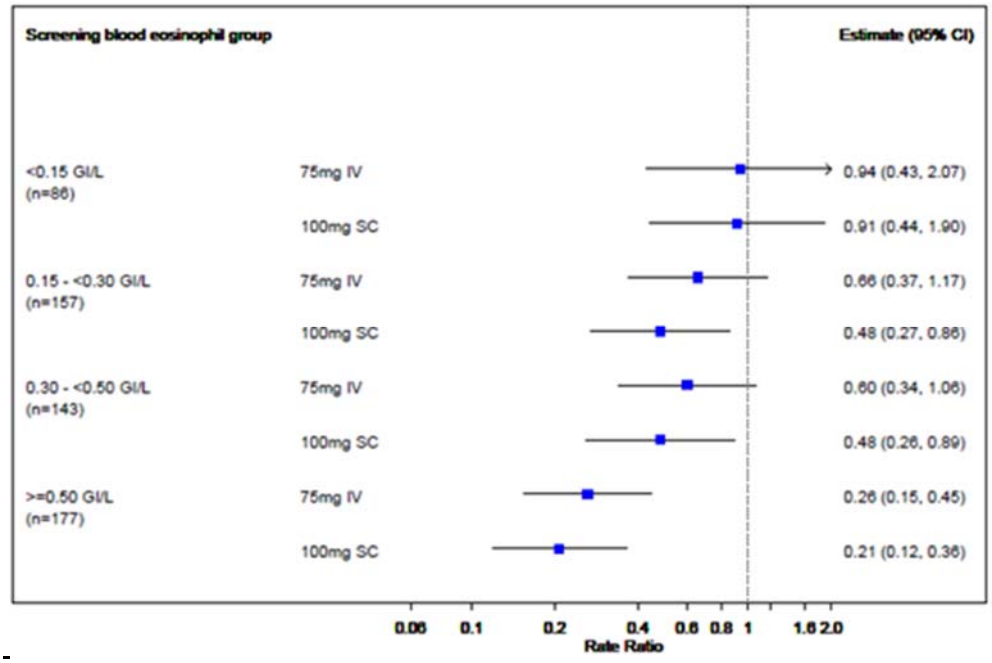


Figure 3: **Rate of Clinically Significant Exacerbations by Screening Blood Eosinophils (MENSA, ITT Population) reproduced from CS Figure 12**



The company's response to the ACD also references a pooled analysis of DREAM and MENSA reported in a conference abstract (Yancey et al. 2016[3]). This showed that the exacerbation reductions for mepolizumab versus placebo based on thresholds of ≥150, ≥300, ≥400 and ≥500 were 52% 59%, 66% and 70% respectively. The more consistent pattern observed here may be due to the analysis of

eosinophil groups with no upper limit (≥150, ≥300, etc.) rather than the specific bands presented in Figures 12 and 13 (150 to 300, 300 to 500, etc.).

The relationship between eosinophil trial inclusion criteria and exacerbations

The ERG report noted that the reduction in exacerbations with mepolizumab was greater in people with an eosinophil count <300 cells/μL in the previous year compared with those with ≥300 cells/μL, which is counterintuitive. The company's response to the ACD notes that there is potentially confounding since all trial patients had eosinophils ≥150 cells/μL at screening and/or ≥300 cells/μL in the previous year. Therefore those with <300 cells/μL in the previous year all had ≥150 at screening whereas those with ≥300 cells/μL in the previous year may have had <150 cells/μL at screening. However, CS Table 20 (adapted in Table 4) illustrates that the results remain counterintuitive when confounding is accounted for. Table 4 is split into three sections. The first section shows that patients with <150 cells/μL at screening and ≥300 cells/μL in the previous 12 months had a poor response to mepolizumab (RR=1.06 and 0.82 for IV and subcutaneous formulations respectively). The second and third sections both relate to patients with ≥150 cells/μL at screening. Within these patients, those with ≥300 cells/μL in the previous year had less favourable RRs (0.60 and 0.46) than those with <300 cells/μL in the previous year (RR=0.28 and 0.26). Therefore, the ERG does not alter their view that the data appear counterintuitive.

Table 4: Rate of Clinically Significant Exacerbations by Blood Eosinophil Inclusion Criteria (MENSA, ITT Population) - adapted from Table 20 of the CS

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

Abbreviations: CI, confidence interval; ITT, intention to treat; IV, intravenous; SC; subcutaneous.

Whether the eligible population should include an eosinophil threshold

The ERG report noted that the subgroup analyses by eosinophil inclusion criteria should be interpreted with caution due to the uncertainties noted above. Therefore the most conservative analysis is probably that which includes all trial patients irrespective of eosinophil threshold, as stated by the Appraisal Committee. However it is worth noting that all patients in the phase III trials met an eosinophil threshold (≥150 cells/μL at screening and/or ≥300 cells/μL in the previous year).

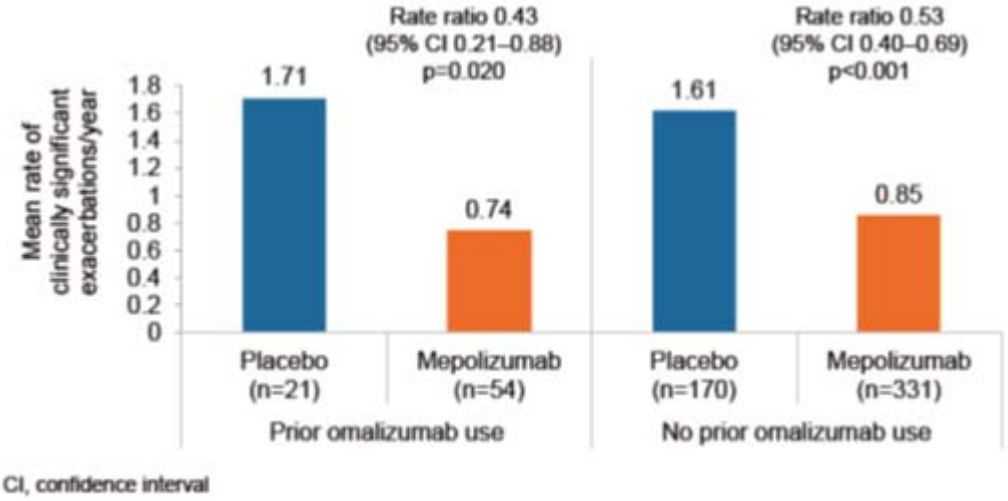
Comparison with omalizumab

The ERG concur with the company that there is uncertainty regarding the relative efficacy of mepolizumab and omalizumab. However, the ERG believes that that the data that would provide the most precise (although still uncertain) estimate would be to use the rate ratios for mepolizumab from SIRIUS and the data for omalizumab for those patients on mOCS.

Patients receiving omalizumab prior to mepolizumab

In MENSA, 13% of patients had received prior omalizumab. Data on patients receiving omalizumab prior to mepolizumab are presented in the CS (Table 48) and in the company's response to the ACD (Figure 7) which is reproduced in Figure 4. There are some differences between these data for reasons the ERG could not ascertain. However, based on Figure 4, the exacerbation rates and rate ratios were very similar for patients with and without prior omalizumab use.

Figure 4: Exacerbation rate by prior omalizumab use (MENSA ITT)



CI, confidence interval

Key Issues

Inclusion of exacerbation rate data from COSMOS

Within the ACD the Appraisal Committee preferred 'setting the exacerbation rates for those meeting the continuation criteria to those seen in the COSMOS study'. The data available to the ERG at the time of the first appraisal did not include the exacerbation rates in COSMOS for those patients who

met the continuation criteria in MENSA, which have now been supplied by the company. These data have been reproduced in
Table 5. The ERG notes that the exacerbation rate for the Committee-preferred population was not provided.

Table 5: Exacerbation rates from COSMOS in patients coming from the mepolizumab arm in MENSA

	ITT	ITT restricted to mOCS (Analysis 1)	≥4 exac or mOCS (Analysis 2)	≥300 eos ≥4 exac or mOCS (Analysis 3)
Meeting CC	0.74	N/A	1.02	1.02
Not meeting CC	3.70	N/A	5.26	5.26

N/A = not available

The Committee considered that "the inclusion of data from COSMOS was preferable, but it was important to separate out the underlying rate of exacerbations with standard care and the relative effect of mepolizumab". The company took two approaches to estimate the underlying rate of exacerbations with standard of care (SoC): the first approach was to use the pre-trial exacerbation rates from MENSA; the second was to use the exacerbation rates from COSMOS in patients who did not meet the continuation criteria in MENSA.

In summary, the exacerbation rates used by the company are the following: for the initial year of the mepolizumab treatment, exacerbation rates from MENSA are used; for patients on SoC or those meeting the continuation criteria, the company use a different approach based on the analysis undertaken.

In Analysis 1, the company uses the same approach as in the CS: For SoC patients the rate observed in the SoC arm in MENSA is used, for patients receiving mepolizumab the rate observed in MENSA in the mepolizumab arm is used for responders, and the rate observed in the SoC used for patients not meeting the continuation criteria.

In Analyses 2 and 3, the exacerbation rates from COSMOS are used for patients on mepolizumab meeting the continuation criteria, with two different approaches used to estimate the exacerbation rates for patients on SoC: using the pre-trial exacerbation rates from MENSA; and using the exacerbation rates from COSMOS in patients who did not meet the continuation criteria in MENSA. Table 6 shows the exacerbation rates used by the company in their analyses.

Table 6: Annual exacerbation rates used by the company in bold, other exacerbation rates provided for reference

	Analysis 1		Analysis 2	Analysis 3
	ITT	ITT restricted to mOCS	≥4 exac or mOCS	≥300 eos ≥4 exac or mOCS
Pre continuation assessment on mepolizumab				
MENSA	**0.88**	**1.43**	**1.36**	**1.34**
Post continuation assessment on mepolizumab				
MENSA	**0.55**	**0.99**	0.77	0.73
COSMOS from MENSA	0.74	N/A	**1.02**	**1.02**
SoC & patients not meeting the continuation criteria				
SoC in-trial MENSA	**1.74**	**2.12**	2.74	2.58
SoC pre-trial MENSA (Approach 1)	3.60	N/A	**5.10**	**5.20**
COSMOS, patients on mepolizumab not meeting CC in MENSA (Approach 2)	3.70	N/A	**5.26**	**5.26**

N/A = not available

The ERG does not agree with the values proposed by the company. Instead the ERG believes the following approaches are more appropriate.

For the initial year, the values from MENSA should be used for both the mepolizumab and the SoC arm. These data reflect what was observed in the trial.

For the rest of the time horizon, the COSMOS data are preferred to MENSA data as these will not be directly correlated to meeting or not meeting the continuation criterion (CC) at the end of MENSA. In contrast using the data from MENSA would force all people who were responders to perpetually have reduced rates of exacerbations and those patients who did not respond would always have an increased rate of exacerbations: in reality it is expected that the rates of exacerbations would fluctuate over time.

Following failure to meet the CC, the rate for those patients discontinuing mepolizumab should be taken from the population who were in MENSA and who did not meet the CC but continued into COSMOS. This value is 3.70 for the intention to treat (ITT) population. The ERG comment that this value is likely to be a lower bound as it is plausible that mepolizumab is still providing some benefit

to the patient and also that the most severe patients who did not meet the CC may not have continued into COSMOS.

Following meeting of the CC, the rate for those patients remaining on mepolizumab should be taken from the population who were in MENSA and continued into COSMOS and who met the CC. This value is 0.74 for the ITT population. The rate assumed for patients who discontinue mepolizumab treatment are discussed later.

For SoC the ideal data for comparison with mepolizumab following the first year are not available. The ERG believes that the best estimate would be derived from the MENSA data as these data provide an average exacerbation rate across the entire cohort. Using the value related to the pre-trial period would have the limitation that any placebo effects or benefits from enhanced monitoring incorporated in COSMOS would be taken into consideration for mepolizumab but no such gain would be provided for SoC. Using a value associated with non-responders in MENSA would have the limitation that SoC would be assumed to have the exacerbation rates associated with the patients who are more severe.

The ERG note that the asthma exacerbations in COSMOS was greater than in MENSA for patients on mepolizumab which could be related to a number of factors including: differences between an RCT setting and that of an open label study; a reduction in the efficacy of mepolizumab; or a combination of both. If the increase in asthma exacerbations were due to the change between an RCT and an open label extension, then the rates of SoC in a setting comparable to COSMOS would be greater than those observed in MENSA. The ERG explored the potential impact of inflating the exacerbation rate in the SoC group from that in MENSA by using the ratio of exacerbations in MENSA and COSMOS for mepolizumab. In MENSA, the exacerbation rate for patients on mepolizumab was 0.88. The ERG estimated using a weighted average based on the percentage of responders (90.9%) and the exacerbation rates in the responder (0.74) and non-responder (3.70) groups, that the exacerbation rate in COSMOS was 1.01. In the ITT population within MENSA, annual exacerbation rates for SoC was 1.74: this was then inflated by a ratio of 1.01/0.88 to estimate an exacerbation rate of 2.00 for SoC patients if they had continued in COSMOS. The same adjustment was performed for the other populations analysed.

For patients meeting the CC who discontinue treatment, the exacerbation rate should be lower than that of SoC, because the most severe subgroup (those failing to meet the CC) has already been excluded. The ERG calculated the rate of exacerbations required in this group in order that if all patients had discontinued mepolizumab the average rates were equal in the SoC and mepolizumab arms. For the ITT population, 9.1% (the percentage not meeting the CC) * 3.70 (the assumed rate in

those not meeting the CC) + 90.9% (the percentage meeting the CC) * 1.84 (the calculated rate for those meeting the CC who discontinue treatment) = 2.00 (the assumed SoC rate beyond the first year).

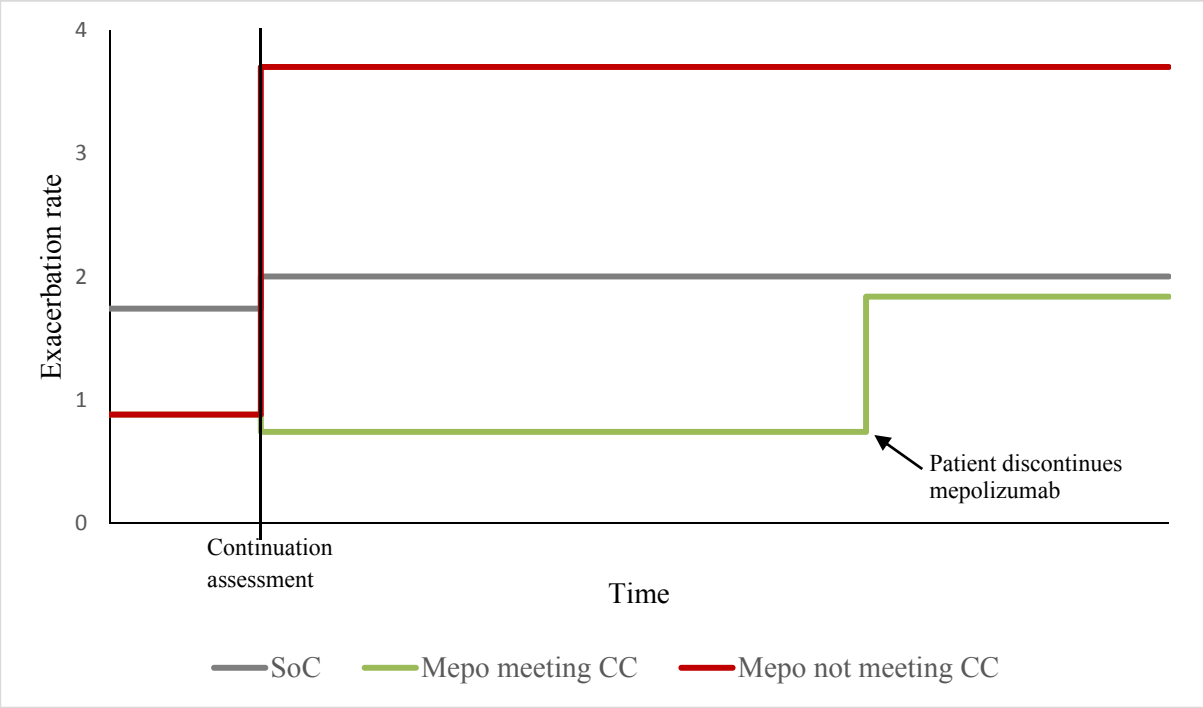
Table 7 includes a summary of the exacerbation rates used by the ERG in its analyses. Figure 5 shows a visual representation of how exacerbation rates change across time for different subgroups.

Table 7: Annual exacerbation rates used by the ERG in bold, other exacerbation rates provided for reference

	Analysis 1		Analysis 2	Analysis 3
	ITT	ITT restricted to mOCS	≥4 exac or mOCS	≥300 eos ≥4 exac or mOCS
Pre continuation assessment on mepolizumab				
MENSA	**0.88**	**1.43**	**1.36**	**1.34**
Post continuation assessment on mepolizumab				
MENSA	0.55	0.99	0.77	0.73
COSMOS from MENSA	**0.74**	**1.33****	**1.02**	**1.02**
SoC – Year 1				
SoC in-trial MENSA	**1.74**	**2.12**	**2.74**	**2.58**
SoC – Years 2 and beyond				
SoC in-trial MENSA adjusted*	**2.00**	**2.44**	**2.95**	**2.84**
Patients on mepolizumab not meeting the continuation criteria				
% of patients not meeting the CC in MENSA	9.1	17.0	10.5	10.8
COSMOS, patients on mepolizumab not meeting CC in MENSA	**3.70**	**3.70*****	**5.26**	**5.26**
Patients discontinuing mepolizumab				
Based on SoC in-trial MENSA adjusted and COSMOS patients on mepolizumab not meeting CC in MENSA****	**1.84**	**2.18**	**2.68**	**2.55**

*Adjusted multiplying by RR between COSMOS and MENSA for all patients on mepolizumab. For "ITT restricted to mOCS" the RR from ITT was used.
**Not provided by the company. Calculated multiplying by the ITT COSMOS/MENSA RR as follows: 0.99 * (0.74/0.55)
***Not provided by the company. Assumed to be equal to ITT
****Not provided by the company. Calculated as: (SoC rate - % not meeting CC * Rate not meeting CC) / (% meeting CC)

Figure 5: Visual representation of exacerbation rates for different subgroups across time



Utilising direct EQ-5D scores in the model

The Appraisal Committee stated that the EQ-5D data from the DREAM study was preferable to the data mapped from the St George's Respiratory Questionnaire (SGRQ) to the EQ-5D using a relationship established in patients with COPD. The company presented no new evidence but reiterated their view that:

1) The SGRQ data were from a larger sample size (n=360) than involved in the DREAM study (n=127) and that the SGRQ data was collected from patients receiving subcutaneous mepolizumab (the licensed formulation) which was not present in the DREAM study but instead used the equivalent intravenous dose.

2) That there were ceiling effects in the EQ-5D as one-third of patients reported perfect health at baseline meaning the it was not possible to observe an improvement in health. The company also hypothesise that this may be because patients have adapted to their ill health and that 'usual activities' may have become normalised'.

3) That mapping the SGRQ to the EQ-5D would alleviate any ceiling effect as the SGRQ is more granular than the EQ-5D and would be more sensitive to a patient's condition than the EQ-5D.

The ERG addresses each point in turn:

1) The ERG does not dispute the facts presented by the company. However, it is unclear to what extent, and in which direction, any difference in the utility would be, between interventions provided intravenously or subcutaneously.

2) The results of the EQ-5D may be explainable due to the 'in the moment' recall period. It is plausible that one-third of patients did not have any problems, on that day, related to any of the five EQ-5D domains. Regarding the adaptation of a patient to ill-health it is expected that this would also apply to a number of other diseases also considered by NICE.

3) The larger sample size associated with the SGRQ dataset is expected to provide a more precise estimate, however, the ERG does not believe that a correct mapping between SGCQ and the EQ-5D would alleviate any ceiling effect of the EQ-5D. If the mapping has been undertaken correctly then it would produce the same proportion of patients with an EQ-5D score of 1 as in the original data set. The typical use of mapping forms a relationship between SGRQ and the mean value of EQ5D: given that the EQ-5D is capped at1, it is therefore expected that the mean value is likely to be below 1 for all values of SGRQ. The use of a linear regression model to map onto a bounded variable (such as the EQ-5D) has been shown to be inappropriate, exhibiting systematic biased estimates away from the midpoint value. Mapping also adds uncertainty even where the estimates are consistent. The problems are likely to be exacerbated by the use of mapping from a different disease area (COPD rather than asthma)

Age related asthma mortality in the model

The Appraisal Committee concluded that the ERG's approach to estimating asthma related mortality was appropriate. The company have cited recent discussions with asthma clinical specialists to state that clinical experience suggested that the mortality rate following an exacerbation was not age-dependent. Furthermore, the company suggest that Roberts et al[2] report the risk of mortality following hospitalisation related to asthma, from any cause, rather than specifically related to asthma, and that this explained the increase with age. The company also state that in Watson et al[1] the authors reported a constant risk of mortality beyond the age of 45 years.

The ERG do not believe the non-anecdotal data support the fact that mortality following an asthma exacerbation is not age-dependent. A critique of the company's views in relation to Roberts et al[2] and Watson et al[1] is provided.

In Roberts et al.[2] the period in which mortality was recorded was 30 days after hospital admission for asthma. Whilst the underlying non-asthma hazard of mortality will, on average, be higher for those of

greater age, the values presented in Roberts et al[2] are markedly higher than those for the general population. For instance, the rate of death in the 30 days following hospitalisation for asthma was 0.45% for people aged 45-54 years and 1.27% for people aged 55-64 years. In contrast, the expected mortality in the general population over a full year is 0.310% and 0.800% for males aged 50 and 60 years respectively (0.216% and 0.523% for females[4]). A weighted average based on the proportion of female admissions reported in Roberts et al.[2] results in 30-day general mortality rates of 0.023% and 0.082% for people aged 45-54 years and 55-64 years respectively. These results, shown in Table 8, suggest that age-differential mortality exists following hospitalisation due to asthma which is only marginally attributable to underlying all-cause mortality rates.

Table 8: Comparison between the mortality rates in Roberts et al.[2] and 30-day general mortality rate

	Age used to calculate general mortality rate for age band	30-day general mortality rate (%)	Mortality after hospital admission according to Roberts et al.[2] (%)
45-54	50	0.020	0.45
55-64	60	0.051	1.27
65+	75	0.218	2.78

The data in Watson et al[1] appear to be, by definition, constant due to the way that the data are reported. No data by subgroups of patients aged 45 years and over are presented to determine whether or not the rate remains constant after 45 years. The ERG comment that as Watson et al[1] show a clear difference in mortality in those aged 18-44 years (0.38%) compared with those aged 45 years and over (2.48%) it is surprising that the clinicians referred to by the company do not believe that age is a factor in estimating the mortality rate post-hospitalisation due to asthma.

The continuation criteria

The CC proposed by the company was that patients whose rate of asthma exacerbations increased whilst on mepolizumab would not continue treatment. The company comments that 'The Committee raised concerns that it may be more appropriate that only those patients whose exacerbation rate improves remain on treatment, and those patients whose exacerbation rate remained stable or worsened discontinue mepolizumab.' The company presented data to show that all of the patients who continued treatment were associated with a reduced rate of asthma exacerbations.

The ERG believes that the data presented by the company showing that all those who continued had a reduced asthma exacerbation rate is an artifact of different lengths of result collection period rather

than a true effect for all patients meeting the CC. To illustrate this point, the baseline patient asthma exacerbation rate was derived from 1 year of observation prior to MENSA. Given that by definition the number of exacerbations are an integer, are typically small and were 2 or more in the preceding 12 months. it would be exceedingly unlikely to have the same rate, over the 32-week period of MENSA. Multiples of 13 exacerbations over a 52 week period and 8 exacerbations over a 32 week period would allow an equal rate in the two periods. It is expected that if both durations were of 52 weeks then a sizeable proportion of patients would have the same rate: if this were not the case then this would assume a low correlation between the number of asthma exacerbations per year.

The company reiterated that patient benefit could still be possible despite no reduction in the asthma exacerbation rate. The ERG had previously conducted analysis to show that if all QALY gain was attributable to chronic well-being that a utility gains of [redacted] and [redacted] would be needed for mepolizumab to have a cost per QALY of £20,000 and £30,000 respectively.

Additional uncertainties

Duration of treatment

The ERG notes that both clinicians consulted by the ERG and expert clinicians present at the committee meeting agreed that they would keep patients on treatment as long as it was effective. The Appraisal Committee also preferred lifelong treatment. The ERG also notes that contrary to the results produced by the company, the impact on the ICER of lifetime treatment is not negligible if asthma related mortality is assumed to be age-related.

Waning of treatment

The company claims that the results from COSMOS show that patients benefit "in terms of asthma control (exacerbation rate) and mOCS reduction without a waning effect". This assertion seems at odds with the sentence in the next paragraph, where they mention the scenario analysis "using a higher exacerbation rate after year 1, as per the data obtained from COSMOS" as a surrogate for a scenario analysis exploring waning effect of mepolizumab, an analysis that was deemed valuable by the Appraisal Committee. The ERG notes that the exacerbation rate reported for those meeting the continuation criteria in MENSA was lower during MENSA (0.55) than in COSMOS (0.74). However, this might be due to other reasons, such as differential effects on exacerbations between an RCT setting or an open label extension setting, or regression to the mean of exacerbation rates for those meeting the continuation criteria.

The attrition rate

The company reported in their response to the ACD the ICERs associated with a range of attrition rates, based on which the company concluded that the impact of the attrition rate on the ICER was

small. However, the ERG notes that if age-dependent asthma related mortality was assumed, the impact of the attrition rate on the ICER may be more substantial, as shown in Table 32.

Table 9: The Impact of lifetime treatment duration and a range of attrition rates on the ICER (MENSA ITT) presented by the company

Attrition rate	ICER (£/QALY)
2%	£31,578
5%	£31,611
10%	£31,670
20%	£31,807
50%	£32,465

Exacerbation rates in those who do not continue mepolizumab treatment

The company discusses the Appraisal Committee's concern regarding the assumption that patients who do not meet the CC are assumed to have an exacerbation rate equal to that of SoC. The ERG notes that the company is equating patients who did not receive mepolizumab treatment with patients who did not meet the CC. The ERG believes that patients not meeting the CC are likely to be a severe subgroup and /or a harder to treat subgroup: this hypothesis is confirmed by the exacerbation rates measured in COSMOS for those who met the continuation criteria in MENSA (0.74) compared with those who did not (3.70). The ERG believes that the most appropriate exacerbation rate for those patients who discontinue mepolizumab treatment due to not meeting the CC would be 3.70.

Age adjusting utilities in the model

The company suggest that any age adjustments applied to the utility of patients within the model 'would be adjusted in all arms by the same amount, and so they would likely cancel out'. The ERG does not believe that this is the case, as there is expected to be a mortality benefit associated with the use of mepolizumab. As such, including age-adjusting utilities to take into consideration that mean utility decreases as people age, would be unfavourable to mepolizumab.

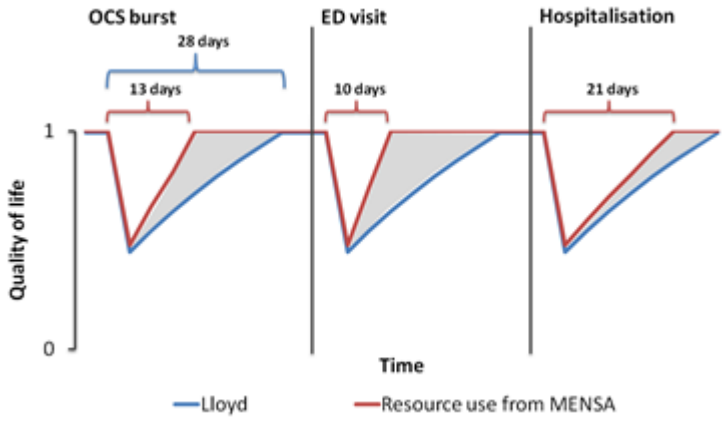
The company further state that 'To apply an age adjusted value for the disutility from an exacerbation would require data on which direction, and which value to age adjust to. In the absence of any data on this, we believe the method applied is appropriate, and thus results based on this assumption would be appropriate.' Whilst the exact change is debatable the ERG believe that a reasonable estimation of the effects of age-adjusting utility would be to set the utility to the minimum of the observed EQ-5D or

the population norm for patients at the corresponding age, that is capping the utility of the patients at the population norm weighted by sex.

Disutilities based on average duration of exacerbations from MENSA

The Appraisal Committee stated that their preferred assumption was to use the duration of utility decrement from the MENSA trial rather than from Lloyd et al,[5] (28 days) as preferred by the company. The company responded that the duration of an exacerbation in the MENSA trial 'was calculated based on the time during which a patient was actively receiving OCS treatment and could underestimate the time during which patients' HRQoL would be affected by an exacerbation.' The company argues that there are likely to be 'a tail end of the exacerbation once resource use has finished, when the utility decrement continued for longer'. This is shown in Figure 6, which has replicated Figure 5 of the company's response to the ACD. The ERG acknowledge that there is potential for the utility to be underestimated using only the duration of increased OCS use. However, applying a 28-day period of disutility would overestimate the loss in utility if the impact on utility was assumed to be related to the key event, such as hospitalisation, as it is expected that the days where a patient was not in hospital would have a higher utility than for the days in hospital. It is plausible that the true disutility could lie between the estimates produced by the two approaches.

Figure 6: Visual representation of using MENSA resource use rather than Lloyd[5] to capture utilities in the model



Benefit of mepolizumab on symptoms

The Appraisal Committee decided that applying a chronic utility gain for being on treatment, over and above that associated with exacerbations, was not appropriate based on testimony from clinical experts. The company responded to this citing two evidence sources

1) That 'in MENSA in the GSK PP, the SGRQ improved from 6.4 to 12.8 units (minimal clinically important difference (MCID) = 4 units), and there was a statistically significant improvement in asthma control (ACQ-5), from 0.42 to 0.96 units (MCID 0.5)'
2) That 'the values for the individual health states in the model were derived from an analysis of the HRQoL of the different groups within MENSA.'

The ERG comment that in the first evidence source these data will be taking into consideration any effects of an asthma exacerbation and thus there will be an element of double-counting. The ERG confirm that the utility differed within MENSA for those on mepolizumab and those patients on SoC. These data were the reasons that the ERG applied differential utilities within the ERG base case in the ERG report.

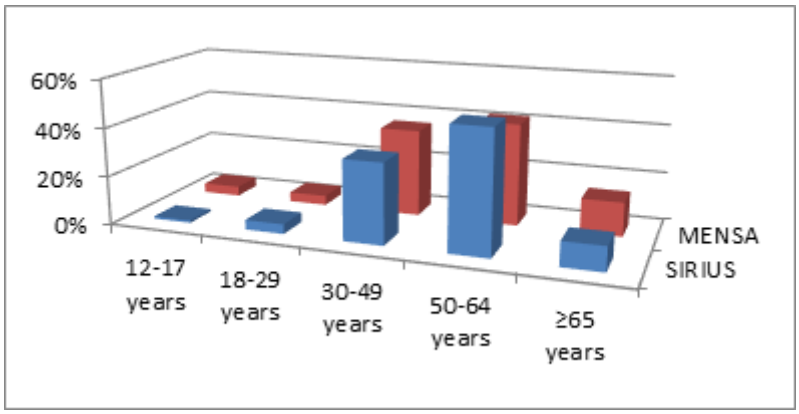
Age in the clinical trials and in the patient population in the UK

Within the ACD the Appraisal Committee 'recognised that the relationship between age and mortality is not linear (see section 4.19), which meant that the starting age was an important driver of the model. The committee was aware that in NICE's technology appraisal guidance on omalizumab for asthma, the results presented were based on a weighted average of the ICERs for different age cohorts to reflect differing mortality risk by age. The Committee therefore considered that variability in age of starting mepolizumab should have been explored in estimating the ICER. The committee concluded

that the age in the model was likely to be older than seen in clinical practice, and adjusting for this would increase the ICER.'

The company responded that the mean age in the model was 50.1 years as this was the mean age in MENSA. The company provided a figure (Figure 6 in their response to the ACD) that showed the age distribution in MENSA and SIRIUS. This is reproduced in Figure 7. The company conclude that 'Given the age ranges in the registry, observational and trial data above, we consider that a starting age of 50.1 years in the model is consistent with the average age seen in clinical practice for these severe asthmatics in England and Wales. Therefore we do not believe this should be considered this a major source of uncertainty.'

Figure 7: Age distribution of patients in MENSA and SIRIUS (reproduced from Figure 6 of the company's response to the ACD)



The ERG believe that the company has misinterpreted part of the comments made within the ACD relating to the model not being linear with respect to age. This means that the expectation of the ICER at the mean age would not be equal to the expectation of the mean ICER were the individual age bands analysed and then combined having been weighted by the numbers in each age category. If the Appraisal Committee maintain their view that mortality following an asthma exacerbation is age-dependent then it is highly likely that the model is non-linear.

Benefits of mepolizumab not captured in the ICER

The company highlighted the fact that the appraisal committee agreed that 'some benefits related to avoiding maintenance OCS use had not been fully captured in the QALY measure and that benefits to carers may not have been captured in the QALY'. The company further stated that 'given the ceiling effects demonstrated in EQ-5D measurements within DREAM (30% of all patients reported perfect health at baseline despite severe disease) the ICER when applying the direct EQ-5D values is not likely to fully capture the quality of life benefits in these patients.'

The ERG comments that it does not necessarily agree that the supposed ceiling effects is a phenomenon that would be unfavourable to mepolizumab. These data show that on a given day that patients were not having problems in any of the five domains of the EQ-5D: mobility; self-care; usual activities; pain / discomfort; and anxiety / depression. It is not clear to what extent the company are stating that the EQ-5D is insufficiently sensitive to measure changes in those with severe asthma. As stated earlier, the ERG does not believe that the mapping from SGRQ to the EQ-5D alleviates any of the alleged limitations of using the EQ-5D within the decision problem.

Factual inaccuracies: Section 3.3 of company response to ACD

The ERG have only commented where it believes that the factual inaccuracies raised are not correct

ACD Section 3.9 Table 3: The ERG believes this table is correct.

ACD Section 3.10: The ERG believes these data on injection site reactions are correct, as stated in the ERG report. These figures were calculated by the ERG across all three RCTs based on the data in the clarification response (question A12). The rates were: mepolizumab subcutaneous 8%, mepolizumab intravenous (all doses) 1.7%, placebo 3.4%.

ACD Section 3.28 Since these are referred to as "disutilities", the ERG believes that omitting the minus sign is correct.

The results presented by the company

Analysis 1 (full ITT and ITT restricted to mOCS)

Table 10: Model results, ITT population, with different maintenance OCS scenarios, with PAS

	Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)
ITT restricted to people on mOCS					
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£31,734**
Full ITT population					

Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£31,659**

The company has presented two scenario analyses within Analysis 1, with the ICERs appearing relatively similar. In the first scenario the analysis is limited to only those patients on mOCS. In the second scenario the full ITT population is analysed.

Analysis 2 (≥4 exac or mOCS)

This analysis has been subjected to sensitivity analyses based on the Appraisal Committee's stated preferences.

These sensitivity analyses were:

1. Using the direct EQ-5D scores from DREAM
2. Assuming a lifetime treatment duration
3. Setting the duration of disutilities based on the duration of an exacerbation in MENSA
4. Using the CC exacerbation rate from COSMOS

The missing ERG exploratory analysis relates to the introduction of an age-related mortality risk following hospitalisation for asthma. As detailed earlier the ERG believes that employed age-related mortality risks are appropriate. In addition to the exploratory analyses conducted by the ERG, the Appraisal Committee also preferred an analysis that did not assume that mepolizumab was associated with a utility gain over and above that imparted through reduce exacerbations.

Two further sensitivity analyses are performed by the company.

5. CC exacerbation rate from COSMOS and SOC exacerbation rate in 12 months prior to entering MENSA
6. CC exacerbation rate and SOC set to non-responders from COSMOS

A combined analysis of sensitivity analyses 1, 2, 3 and 5 were also presented. The results for Analysis 2 are presented in Table 11.

Analysis 3 (≥4 exac or mOCS and eosinophils ≥300/µl).

Analysis 3 contains the population preferred by the company. The same sensitivity analyses as explored in Analyses 2 were performed in Analyses 3. These results are provided in Table 12.

Table 11: Results of analysis 2: need for continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year), base case and scenario analyses (with PAS)

Sensitivity analysis		GSK sub-population				
		Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)
N/A	Base-case					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£22,305
1	Direct EQ-5D scores					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£27,916
2	Lifetime treatment duration					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£22,569
3	Duration of an exacerbation from MENSA rather than Lloyd[5]					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£22,888
4	CC exacerbation rate from COSMOS (1.02), SOC MENSA in-trial (2.74)					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£24,105
5	CC exacerbation rate from COSMOS (1.02), SOC MENSA pre-trial (5.10)					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£14,788
6	CC exacerbation rate (1.02), SOC set to non-responders from COSMOS (5.26)					

	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£14,484**
Combined	**Combined analysis using 1-3 and 5**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£17,327**

Table 12: Results of analysis 3: blood eosinophil level ≥300 cells/µl in the last year, and need for continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year), base case and scenario analyses (with PAS)

Sensitivity analysis		GSK sub-population				
		Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)
N/A	Base-case					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£22,134
1	Direct EQ-5D scores					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£28,949
2	Lifetime treatment duration					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£22,363
3	Duration of an exacerbation from MENSA rather than Lloyd[5]					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£22,674
4	CC exacerbation rate from COSMOS (1.02), SOC MENSA in-trial (2.58)					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£24,273
5	Post CC rate from COSMOS (1.02), SOC MENSA pre-trial (5.20)					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	£14,149
6	Post CC rate (1.02) and SOC set to non-responders from COSMOS (5.26)					

	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£14,043**
Combined	**Combined analysis using 1-3 and 5**					
	Mepo	[redacted]		[redacted]		
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	**£16,798**

The results of the ERG's exploratory analyses

The ERG undertook exploratory analyses based on the Committee's preferred assumptions and including the new evidence provided by the company in their response. The ERG undertook a base case analysis and a set of scenario analyses the Committee deemed valuable in the ACD. Table 13 shows the differences between the assumptions and parameters used in the company's and ERG's analyses.

Table 13: Different assumptions and parameters used in the company's and the ERG's analyses

Parameter	**Company's analyses**	**ERG's analyses**
Mortality	Watson *et al*.[1]	Watson *et al*[1] age adjusted using Roberts *et al*[2]
Utility source	SGRQ mapped to EQ-5D (MENSA)	No utility gain for being on treatment (average EQ-5D between SoC and mepolizumab used for all states)
Duration of exacerbations	28 days (as per Lloyd *et al*.[5])	Mean duration in MENSA
Duration of treatment	10 years	Lifetime
Age-adjusted utilities	No	Yes
Exacerbation rates	See Table 6	See Table 7

Base case with the Appraisal Committee's preferred assumptions

Analysis 1 - ITT and ITT restricted to people on mOCS

Table 14: Results of the ERG's analysis 1 (deterministic)

	Total cost	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**
ITT restricted to people on mOCS					
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£107,499
ITT					
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£92,500

Analysis 2 - continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)

Table 15: Results of the ERG's analysis 2 (deterministic)

	Total cost	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£57,708

Analysis 3 - blood eosinophil level ≥300 cells/µl in the last year and continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)

Table 16: Results of the ERG's analysis 3 (deterministic)

	Total cost	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£59,859

Scenario analyses

Using the unadjusted exacerbation rates for SoC taken from MENSA

For its base case analysis, the ERG adjusted the exacerbation rate for SoC by multiplying the exacerbation rate measured in MENSA in patients on SoC by the RR calculated between the exacerbation rates from MENSA and COSMOS for patients receiving mepolizumab. The ERG undertook an alternative scenario analysis where the exacerbation rate from MENSA was used for SoC in all cycles. As expected, the ICERs increased.

The ERG comment that although these analyses do not directly affect the exacerbation rates for patients receiving mepolizumab, there is an indirect effect on the mepolizumab results as patients are assumed to have the SoC rate after discontinuing.

Analysis 1

Table 17: Results of the ERG's analysis 1 (deterministic)

	Total cost	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**
ITT restricted to people on mOCS					
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£150,668
ITT					
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£114,217

Analysis 2 - continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)

Table 18: Results of the ERG's analysis 2 (deterministic)

	Total cost	**Δ Costs**	**Total QALYs**	**Δ QALYs**	**ICER (vs.)**
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£63,366

Analysis 3 - blood eosinophil level ≥300 cells/µl in the last year and continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)

Table 19: Results of the ERG's analysis 3 (deterministic)

	Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£67,832

Using EQ-5D utilities from the DREAM study

The Appraisal Committee concluded that it was inappropriate to include different utilities in "on" and "off" treatment health states that captured further quality of life benefits than reducing exacerbations. However, the ERG undertook a scenario analysis using the EQ-5D scores captured in the DREAM trial.

Analysis 1 - ITT and ITT restricted to people on mOCS

Table 20: Results of the ERG's Analysis 1 (deterministic)

	Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)
ITT restricted to people on mOCS					
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£64,216
ITT					
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£63,388

Analysis 2 - continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)

Table 21: Results of the ERG's analysis 2 (deterministic)

	Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£48,358

Analysis 3 - blood eosinophil level ≥300 cells/µl in the last year and continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)

Table 22: Results of the ERG's analysis 3 (deterministic)

	Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£50,960

Waning effect

The Appraisal Committee considered that a scenario exploring a waning effect of mepolizumab would be valuable: this was not provided by the company. The ERG undertook a scenario analysis where it was assumed that the treatment effect of mepolizumab (i.e. exacerbation rate reduction) would linearly diminish until losing all its effect at the end of a certain period, denoted the treatment effect duration. Therefore, in the beginning, the patients who meet the continuation criteria have the same exacerbation rates as in the base case analysis; mid-way through the treatment effect duration patients will have the average exacerbation rate between that of the base case analysis and that of mepolizumab discontinuers; and at the end of the treatment effect duration patients are assumed to have the same exacerbation rates as mepolizumab discontinuers. It is assumed that all patients discontinue treatment at the end of the treatment effect duration. If this does not happen then the ICERs would be favourable to mepolizumab. In Table 23 to Table 26 the ICERs of mepolizumab vs. SoC are shown for a range of different treatment effect durations (5 years to 30 years). The results assuming no waning effect are presented to highlight the impact on waning effects on the ICER.

Table 23: ICERs (£/QALY) for mepolizumab vs. SoC for the ITT population for different treatment and waning durations

Treatment duration	No waning	Waning
5 years	£138,356	£218,108
10 years	£105,280	£188,693
20 years	£94,494	£146,192
30 years	£92,495	£126,072
Lifetime	£92,500	-

Table 24: ICERs (£/QALY) for mepolizumab vs. SoC for the ITT population restricted to people on mOCS for different treatment and waning durations

Treatment duration	No waning	Waning
5 years	£148,346	£217,026
10 years	£119,761	£201,689
20 years	£109,539	£162,851
30 years	£107,508	£142,476
Lifetime	£107,499	-

Table 25: ICERs (£/QALY) for mepolizumab vs. SoC for patients on continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year) for different treatment and waning durations

Treatment duration	No waning	Waning
5 years	£82,421	£127,294
10 years	£64,788	£113,783
20 years	£58,880	£89,718
30 years	£57,716	£77,869
Lifetime	£57,708	-

Table 26: ICERs (£/QALY) for mepolizumab vs. SoC for the ITT population restricted to people on mOCS for different treatment and waning durations

Treatment duration	No waning	Waning
5 years	£83,352	£125,812
10 years	£66,689	£115,082
20 years	£60,982	£91,967
30 years	£59,858	£80,179
Lifetime	£59,859	-

Weighted average of different age bands

The ERG undertook a scenario analysis where it performed a weighted average of estimated QALY gains and additional costs for each age band weighted according to its prevalence in the MENSA population. The distribution of the population across different age bands was taken from Figure 5 of the company's response to the ACD. For each age band, the model was run setting the starting age to the middle point between the bounds of the band. The age bands, their prevalence and the starting age used for its band are shown in Table 27. Interestingly, even if the ICER is not linear with respect to age (see Table 28, for example), the weighted average ICER falls very close to that of the base case analysis for all populations.

Table 27: Age bands, their prevalence in MENSA and the centre age for each band

Age band	% of the population	Centre age of the band
12-17	4	15*
18-29	4	24
30-49	36	40
50-64	42	57.5
>=65	14	69.9**

*Used 20 instead because the model did not support a lower age
**Calculated so that the weighted average would match the mean starting age (50.1 years)

Analysis 1 - ITT and ITT restricted to people on mOCS

Table 28: Results for each age band for the ITT population (deterministic)

Age band	**Costs**			**QALYs**			**ICER (vs.)**
	Mepolizumab	**SoC**	**Incr.**	**Mepolizumab**	**SoC**	**Incr.**	
12-17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£345,852
18-29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£329,044
30-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£168,217
50-64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£65,709
>=65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£61,596

Table 29: Results of the ERG's analysis 1 (deterministic)

	Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)
ITT restricted to people on mOCS					
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£107,272
ITT					
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£92,786

Analysis 2 - continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)

Table 30: Results of the ERG's analysis 2 (deterministic)

	Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£57,633

Analysis 3 - blood eosinophil level ≥300 cells/µl in the last year and continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year)

Table 31: Results of the ERG's analysis 3 (deterministic)

	Total cost	Δ Costs	Total QALYs	Δ QALYs	ICER (vs.)
Mepo	[redacted]		[redacted]		
SoC	[redacted]	[redacted]	[redacted]	[redacted]	£60,172

Attrition rates

The company claimed that the impact of the attrition rate on the ICER was negligible. The ERG argued that this was the case only when assuming asthma related mortality remained constant after the age of 45 and undertook scenario analyses with a range of different attrition rates based on its base

case. The results in Table 32 show that the ICER increases noticeably when considering higher attrition rates.

Table 32: Impact on the ICER of a range of different attrition rates according to the ERG's base case. The company's result provided for reference

Attrition rate	ICERs (£/QALY) based on the company's base case	ICERs (£/QALY) based on ERG's base case
0%	£31,418	£76,032
2%	£31,578	£78,585
5%	£31,611	£83,347
10%	£31,670	£92,254
20%	£31,807	£107,450
50%	£32,465	£116,533

REFERENCES

1. Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: A national United Kingdom database analysis. *Respiratory Medicine* 2007;**101**:1659-64. http://dx.doi.org/10.1016/j.rmed.2007.03.006
2. Roberts NJ, Lewsey JD, Gillies M, Briggs AH, Belozeroff V, Globe DR*, et al.* Time trends in 30 day case-fatality following hospitalisation for asthma in adults in Scotland: A retrospective cohort study from 1981 to 2009. *Respiratory Medicine* 2013;**107**:1172-7. http://dx.doi.org/http://dx.doi.org/10.1016/j.rmed.2013.04.004
3. Yancey S, Myer B, Gunsoy N, Keene O. Exacerbation Reduction in Severe Eosinophilic Asthma Based on Eosinophil Thresholds. *Journal of Allergy and Clinical Immunology* 2016;**AB208**.
4. National Life Tables: United Kingdom. 2016, https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.
5. Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Primary Care Respiratory Journal* 2007;**16**:22. http://dx.doi.org/10.3132/pcrj.2007.00002