HIGHLY CONFIDENTIAL

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. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - GlaxoSmithKline
   - Asthma UK
   - NHS England
   - Novartis

   The Department of Health indicated that they had no comments

3. **Comments on the Appraisal Consultation Document from experts:**
   - Professor Andrew Wardlaw – clinical expert, nominated by the Royal College of Physicians

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

5. **Evidence Review Group's critique of the company's response to the ACD2**
   - ERG's critique of the company's response to the ACD2
   - Comment on factual inaccuracies reported by the company

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Mepolizumab for treating severe refractory eosinophilic asthma

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
GSK UK LTD	**Executive Summary** GSK appreciates the opportunity to respond to the second ACD (ACD2) and to submit additional evidence for discussion at the next appraisal committee meeting (ACM), which we believe will address uncertainties and questions raised by the committee. Whilst we are disappointed that negative interim guidance has been issued for mepolizumab for a second time, GSK is reassured by the agreement of an appropriate population for guidance (henceforth referred to as the 'accepted population': ≥300 cells/μLin the previous year and 4 or more exacerbations in the previous year or on maintenance OCS), and that NICE has recognised the: • Substantial morbidity in the severe eosinophilic asthma population and the need for alternative treatments (ACD Section 4.1) • Clinical efficacy of mepolizumab at reducing clinically significant exacerbations (ACD Section 4.9) • Degree of innovation and benefits not reflected in the ICER: the reduction in dependency on oral corticosteroid use and potential benefits to carers provided by this medicine (ACD Section 4.28). It is anticipated that mepolizumab would be appropriate and available to only a relatively small number of severe asthma patients, already under the care of a specialist asthma centre. At present there are very limited treatment options for these patients and they remain at risk of frequent but unpredictable asthma attacks (exacerbations) that can lead to recurrent unscheduled hospital attendances, admissions and/or death. GSK has considered the committee's conclusions and concerns in ACD2, and taken steps to generate new data, conduct further analyses, revise model inputs and offer an improved PAS to address the outstanding concerns. These new elements, together with most of the adjustments to assumptions made by the committee, give a revised company base-case, detailed in this response and summarised below. Summary of the key new elements introduced • The committee concluded that mepolizumab did not demonstrate benefit beyond that provided by the reduction in exacerbations (Section 4.23). GSK strongly	Thank you for your comment. After considering the comments received in response to the ACD2 in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD. The committee's full considerations for each issue are outlined in section 4 of the FAD.

Consultee	Comment [sic]	Response
	refute this conclusion and in our response we provide new analyses, alongside existing data, which demonstrates the health related quality of life (HRQoL) and symptom benefit of mepolizumab. In addition, the benefits of mepolizumab beyond exacerbation reduction were supported by asthma experts in the clinical community in their response to the previous ACD. We therefore ask the committee to reconsider its position and accept mepolizumab is associated with an impact on HRQoL and symptoms over and above a reduction in exacerbations, and that this benefit should be included when determining the committee's most plausible ICER. • Recognising the committee's preference to use directly derived EQ-5D values from the Phase IIb DREAM study rather than mapped EQ-5D from SGRQ values within the Phase III MENSA trial (section 4.22), our revised base case uses the directly derived data; the data are adjusted for differences in EQ-5D at baseline in the agreed sub-group between the add-on mepolizumab and SoC arms. • To respond to the committee's preference of stratifying asthma-related mortality into narrower age bands, a retrospective data analysis was conducted, with analyses by age band (section 4.24), including for those over the age of 45. This analysis confirmed the committee's view that there is increasing asthma mortality over the age of 45 years and has been included in our updated base case. • In line with the committee's preference for a continuation criteria based on improvement (section 4.15) and clinician feedback in response to the first ACD, a more explicitly defined continuation criteria has been proposed, consistent with the mepolizumab license and clinical trial data. We propose two alternative exacerbation reduction thresholds for the committee to consider; 50% which is suggested by severe asthma clinicians, or 30% which is aligned to the available literature on a clinically meaningful reduction in exacerbations. The proposed wording for the criteria is: • Mepolizumab therapy should be continued if at 12 months from initiation of treatment : – A 50% (or 30%) reduction in the number of exacerbations is observed compared to the prior 12 months OR – A reduction in maintenance oral corticosteroid dose is observed while maintaining asthma control • Whilst GSK considers that the initial PAS price offered was fair and represented good value for money to the NHS, in order to improve the cost-effectiveness further, an improved PAS has been submitted by GSK. Based on the new data and analyses provided, the original continuation criterion and new PAS, the ICER is £31,724 per QALY gained. With the revised continuation criteria	

Consultee	Comment [sic]	Response
	at 50% exacerbation reduction, the base case ICER is £27,418 per QALY gained. Using a 30% exacerbation reduction for the continuation criteria, the ICER would slightly increase to £28,398 per QALY gained. Accounting for the additional steroid-sparing benefits of mepolizumab not fully captured in the model (and recognised as critical by clinicians in their treatment decisions) could reduce the ICER further by £4,000-£9,000, using results previously applied in omalizumab appraisal TA278. GSK is concerned that mepolizumab is not being considered as an alternative to omalizumab in patients eligible for both medicines (Section 4.10). In the small overlap population clinicians should be able to prescribe the medicine that is most appropriate for people based on their phenotype as described in the ACD – if final guidance remains negative this would not be the case. Allowing mepolizumab as an alternative to omalizumab would have no opportunity cost to the NHS, as with the revised PAS mepolizumab is likely to be a cost saving option. This should be considered in the context that the assumptions applied to the mepolizumab appraisal are more conservative than those used in the omalizumab appraisal (TA278). Applying the TA278 assumptions to mepolizumab improves its cost effectiveness. The response that follows provides more detail on the revised company base case, data inputs used, and the corresponding results. We hope that with the provision of these additional analyses and the revised PAS price, the committee will recognise the value of mepolizumab to patients in England and Wales by issuing a positive recommendation for this small subgroup of severe asthma patients.	
GSK UK LTD	**Has all the relevant evidence been taken into account? Are the recommendations sound and a suitable basis for guidance to the NHS?** After carefully considering the second ACD, we provide our responses together with new data, which results in a revised company base case incorporating the updated PAS. Overall, there is mutual agreement for nearly all elements and a brief rationale is provided where variance exists. Section 1 follows and sets out the details supporting the rationale for the revised company base case. Section 2 presents the cost effectiveness results utilising the new base case assumptions. Table 1 Revised company base case Key: ✓ = preferred and incorporated by committee / included in GSK base case R = raised but not included in committee base case A = not incorporated in GSK base case & alternative proposed	Thank you for your comment. After considering the comments received in response to the ACD2 in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD. The committee's full considerations for each issue are outlined in section 4 of the FAD.

Consultee	Comment [sic]				Response
	Assumption in ACD	ACD2 preferred assumption	Revised company base case	i) Justification ii) Section in response	
	Patient population (ACD section 4.7 & 4.13) people with a blood eosinophil count of ≥300cells/μL in the previous year and at least one of the following: • 4 or more exacerbations in the previous year • on maintenance oral corticosteroids	✓	✓	i) Agree ii) N/A	
	Treatment duration (ACD section 4.20) Lifetime	✓	✓	i) There is uncertainty on treatment duration in this chronic condition ii) N/A	
	Exacerbations rates (ACD section 4.16-4.19) Source of exacerbation rates to be used post application of continuation criteria as per ERG proposals and committee's preference.	✓	✓	i) Revised company base case utilises ERG approach preferred by the committee is considered reasonable ii) N/A	
	Duration of an exacerbation (ACD section 4.23) Taken from MENSA relates to the timing of resource utilisation	✓	A	i) ERG and company believe that in reality the duration will be somewhere between Lloyd and	

Consultee	Comment [sic]				Response
				MENSA, so propose midpoint ii) Section 1.1	
	Effect on symptoms (ACD section 4.23) No effect obtained on top of exacerbations	✓	A	i) Company disagrees. Data show that there is an impact on symptoms ii) Section 1.2	
	Directly Elicited EQ-5D (ACD section 4.22) Preferred to SGRQ	✓	✓	i) Recognise the committee's preferences for direct EQ-5D. Baseline adjusted values presented ii) Section 1.3	
	Age adjusted utility (ACD section 4.23) Utility adjusts with age	✓	A	i) Trial data show that there is no evidence of utility being affected by age ii) Section 1.4	
	Age adjusted mortality (ACD section 4.24) There is an impact of age on asthma related mortality	✓	✓	i) New data shows that there is an impact of age on asthma mortality ii) Section 1.5	
	Age (ACD section 4.25) Model start age of 50.1years	R	✓	i) The committee noted that the impact on the ICER was marginal, so maintained at 50.1 ii) Section 1.7	
	Continuation Criteria: (ACD section 4.15) • original • 50%	R	✓	i) Reflects the committee's preference for a continuation criteria	

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<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>
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<tr><td>• 30%</td><td></td><td></td><td>linked to improvement
ii) Section 1.6</td></tr>
<tr><td>mOCS benefit (ACD section 4.28)</td><td>R</td><td>✓</td><td>i) Tries to quantify the benefits of avoiding mOCS use. Included as a separate scenario to base case.
ii) Section 1.7</td></tr>
</table>
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<tr><td>GSK UK LTD</td><td>
Duration of exacerbations
<table>
<tr><th>Assumption in ACD</th><th>ACD2 preferred assumption</th><th>Revised company base case</th><th>Justification</th></tr>
<tr><td>Duration of exacerbation (ACD section 4.16-4.19)
Taken from MENSA; relates to the timing of resource utilisation</td><td>✓</td><td>A</td><td>ERG and company believe that in reality the duration will be somewhere between Lloyd and MENSA, so propose midpoint</td></tr>
</table>
In ACD section 4.23, it states that the ERG suggests incorporating the average length of exacerbations as measured in the MENSA trial, and that the committee considered this appropriate. However, this conclusion did not fully reflect our understanding of the ERG report and discussion at the committee meeting.
In its critique of the company's response to the first ACD (ACD1), the ERG acknowledged that there is potential for the utility to be underestimated using only the average length of exacerbations in MENSA, as this duration was defined by increased OCS use and not the time period during which HRQoL would be impaired. The company response to ACD1 explained that this is because there would be a tail end of the exacerbation once healthcare resource utilisation had ceased, when the utility decrement continued for longer, giving a censored duration of an exacerbation. The ERG considered that applying a 28-day period of disutility (as per Lloyd) and originally recommended by GSK, would overestimate the loss in utility if the impact on utility was assumed to be related to the key event. The ERG considered that
</td><td>The committee's considerations about the duration of exacerbations are outlined in the FAD. The committee concluded that the company's alternative approach to estimating the duration of disutility associated with an exacerbation, presented in response to the second appraisal committee meeting, was appropriate(see section 4.19 of the FAD).</td></tr>
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<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>
'it is plausible that the true disutility could lie between the estimates produced by the two approaches' (ERG critique of company response to ACD1, page 19).
This issue was discussed at the second Appraisal Committee Meeting (ACM2) where both the ERG and GSK proposed that the duration could feasibly be between MENSA and Lloyd.
In response to the comments by the ERG and the discussions in ACM2 that the duration of an exacerbation could be between the two sources, in the revised company base case, the model uses the midpoint between MENSA and Lloyd for the duration of exacerbations, as set out in Table 2.
Table 2 Duration of exacerbations (days) and midpoint used in revised company base case
<table>
<tr><th>Type of exacerbation</th><th>MENSA</th><th>Lloyd</th><th>Midpoint – revised company base case</th></tr>
<tr><td>OCS burst</td><td>12.7</td><td>28</td><td>20.3</td></tr>
<tr><td>ED visit</td><td>10.4</td><td>28</td><td>19.2</td></tr>
<tr><td>Hospitalisation</td><td>20.7</td><td>28</td><td>24.4</td></tr>
</table>
This revised assumption for the duration of an exacerbation, which utilises a midpoint between two sources, remains a conservative assumption relative to that used in omalizumab (TA278). Here the source of duration of an exacerbation was changed from the trial duration to Lloyd by the Assessment Group, the opposite of what is proposed by the committee here.
We therefore believe that taking the midpoint is a pragmatic approach and may still be a conservative estimate.
</td><td></td></tr>
<tr><td>GSK UK LTD</td><td>
Effect on symptoms
<table>
<tr><th>Assumption in ACD</th><th>ACD2 preferred assumption</th><th>Revised company base case</th><th>Justification</th></tr>
</table>
</td><td>The committee's considerations about the effect of treatment on symptoms are outlined in the FAD. The committee concluded that mepolizumab probably improves symptoms as well as reducing exacerbation rates (see section 4.19 of the FAD).</td></tr>
</table>

Consultee	Comment [sic]	Response

Effect on symptoms No effect obtained on top of exacerbations	✓	**A**	Data show that there is an impact on symptoms

Section 4.23 of the ACD mentions that:

'the committee heard from the clinical experts that mepolizumab was unlikely to have an effect on symptoms. That the company disagreed, but was unable to provide any evidence that mepolizumab is associated with an impact on symptoms over and above a reduction in exacerbations. The committee concluded that an on-treatment utility gain was inappropriate'.

GSK strongly refute this conclusion; both the ERG at ACM2 and the feedback to ACD1 from severe asthma experts support that mepolizumab has a benefit on symptoms beyond exacerbation reduction:

- In its report, the ERG explains the data set out by GSK, which shows a difference between mepolizumab and standard of care in SGRQ and ACQ-5, and explains that the model states are informed by analyses of patient level HRQoL data from the trials. Further the ERG explains that these data were the reason why the ERG applied differential utilities within the ERG base case in its report.

- Experts who responded to ACD1 (including those in the severe asthma clinical community from the 10 severe asthma BTS centres), clearly stated that mepolizumab has a symptom benefit, and challenges the committee's view that there is no evidence to support benefit of mepolizumab beyond that experienced from an improvment in exacerbation rate. This is consistent with feedback we received from clinicians who treated patients as part of the mepolizumab clinical trial programme.

Notwithstanding that mepolizumab has been acknowledged as being very effective at reducing clinically significant exacerbations, it is highly unlikely that this in isolation would cause the clinically meaningful size of improvement seen in the ACQ and the SGRQ and non-specific question to both physician and subjects about their impression of the overall evaluation of treatment response. This is supported by mepolizumab's mechanism of action as an anti-IL5 treatment, reducing eosinophilic inflammation. As presented in the company submission, by reducing the inflammatory aspects of

Consultee	Comment [sic]	Response
	asthma, mepolizumab improved symptom control, quality of life and lung function, in addition to reducing the risk of clinically significant exacerbations in the clinical trials. To further demonstrate the benefit of mepolizumab on top of exacerbations, below we present: • ACQ and SGRQ data with new analyses on SGRQ data showing the benefit of mepolizumab therapy over and above the benefit experienced from a reduction in exacerbations • Subject- and clinician-rated overall evaluation of response & other measures ***1.2.1. SGRQ and ACQ Data & Analyses*** The St George's Respiratory Questionaire (SGRQ) has three domains (listed below) and the minimal clinically important difference (MCID) is 4 points. 1. frequency of respiratory symptoms 2. daily physical activity score 3. measuring impact on daily life The ACQ-5 questionnaire asks about the symptoms listed below, and a change or difference in score of 0.5 is considered to be the MCID. 1. woken at night by symptoms 2. wake in the mornings with symptoms 3. limitation of daily activities 4. shortness of breath 5. wheeze ***ACQ and SGRQ total score: existing HRQoL data*** As previously presented for MENSA, the accepted sub-population had a significant disease burden at baseline with an ACQ-5 score of 2.3 (>1.5 is considered to be inadequately controlled asthma and an SGRQ score of 49.9 (100mgSC/75mgIV) (Table 3), despite being optimised on high dose asthma therapy. Mepolizumab was able to demonstrate a clinically and statistically significant benefit in quality of life (SGRQ) and asthma control (ACQ) greatly above the MCID of 4 and 0.5, respectively, from baseline and versus placebo (Table 4). **Table 3 Baseline ACQ-5 and SGRQ scores, for accepted population, MENSA**	

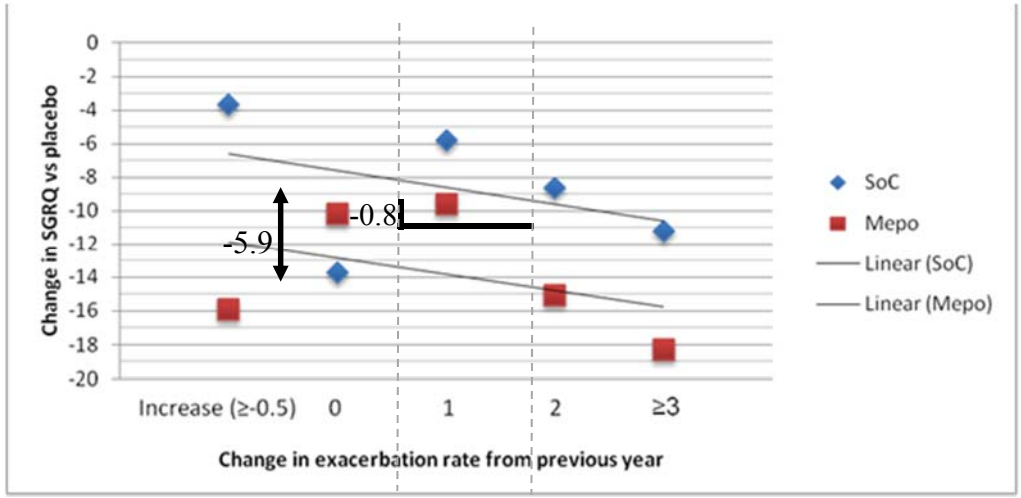
Consultee	Comment [sic]	Response

		Placebo	Mepo 75mg IV/100mg SC
Baseline ACQ-5 Mean Score	N	68	171
	Mean (SD)	**2.5 (1.30)**	**2.3 (1.25)**
	Median (Min, Max)	2.5 (0, 6)	2.4 (0, 5)
Baseline SGRQ Total Score	N	68	174
	Mean (SD)	**51.7 (19.46)**	**49.9 (18.41)**
	Median (Min, Max)	52.6 (15, 95)	51.3 (5, 90)

Table 4 Change in ACQ-5 and SGRQ scores at 32 weeks, for accepted population, MENSA

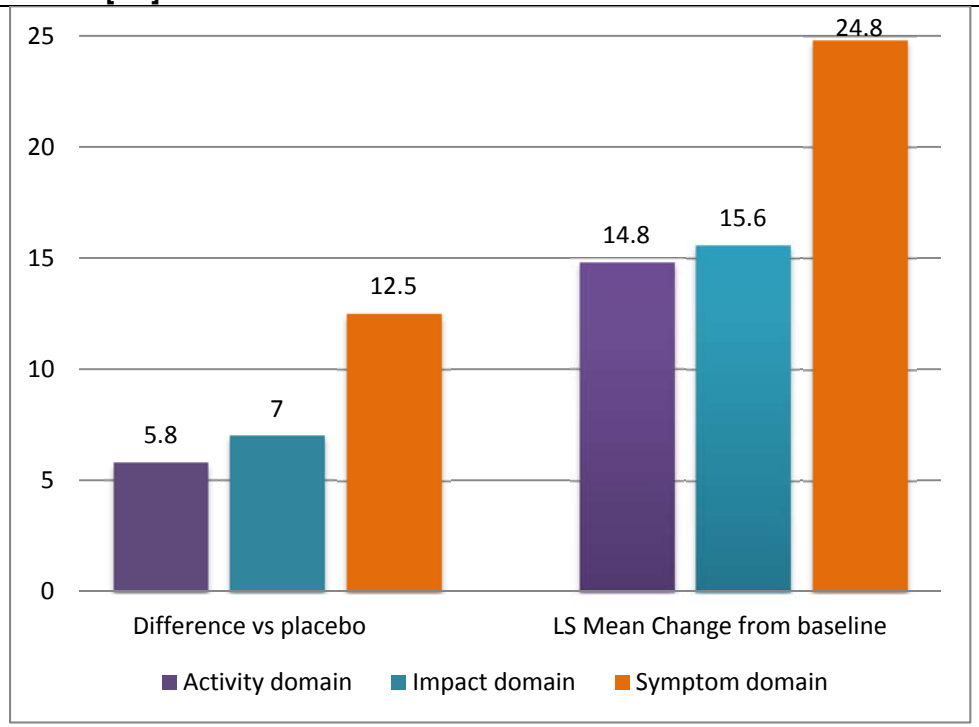
		Placebo	Mepo 100mg SC	Mepo 75mg IV
ACQ	N	62	88	69
	LS Mean (SE)	1.97 (0.114)	1.32 (0.097)	1.4 (0.108)
	LS Mean Change (SE)	**-0.37 (0.114)**	**-1.02 (0.097)**	**-0.94 (0.108)**
Comparison vs placebo	**Difference**		**-0.65**	**-0.57**
	95% CI		-0.95, -0.36	-0.88, -0.26
	p value		<0.001	<0.001
SGRQ	N	64	91	73
	LS Mean (SE)	40.9 (2.04)	33.2 (1.71)	33.3 (1.92)
	LS Mean Change (SE)	**-9.4 (2.04)**	**-17.1 (1.71)**	**-17.0 (1.92)**
Comparison vs placebo	**Difference**		**-7.7**	**-7.6**
	95% CI		-13, -2.5	-13.2, -2.1
	p value		0.004	0.007

SGRQ – new analysis: isolating the benefit on HRQoL over and above exacerbation rate reduction

Consultee	Comment [sic]	Response
	A new analysis was performed looking at the quality of life benefit patients experienced after adjusting for any change in exacerbation rate and the associated SGRQ benefit (analysis of covariance with covariates of baseline SGRQ, absolute reduction in exacerbations versus previous year, and treatment to predicted estimates change in SGRQ independent of exacerbation reduction). This was done in the MENSA ITT population to maximise the potential sample size. In this analysis, mepolizumab (100mg SC & 75mg IV) showed a clear and clinically meaningful quality of life benefit in SGRQ of -5.9 (95% CI -8.7,-3.1), independent of the impact of a reduction in exacerbations when compared to placebo (Figure 1). The impact on SGRQ of reducing the rate of exacerbations by 1 exacerbation per year was an improvement of 0.8 points (95% CI -1.3,-0.3) per exacerbation reduced. Therefore although part of the QoL benefit for patients on mepolizumab will be due to a reduction in exacerbations, there is HRQoL benefit from add-on mepolizumab therapy over and above this. **Figure 1 Change from baseline SGRQ by absolute reduction in exacerbations compared to previous year (100mg SC & 75mg IV combined, ITT MENSA)**  Note: Predicted estimates obtained using analysis of covariance with covariates of base, absolute reduction in exacerbations versus previous year, and treatment (Change in exacerbation rates in previous year 0 = -0.5 to <0.5, 1 = 0.5 to <1.5, 2 = 1.5 to <2.5, ≥3 = ≥2.5).	

Consultee	Comment [sic]	Response
	We recognise this is an exploratory analysis however the extent of the symptom benefit observed from add-on mepolizumab, beyond that resulting from a reduction in exacerbations, supports clinical feedback and clinical trial data - that the QoL benefits are not only due to a reduction in exacerbations. ***SGRQ – new analysis: domain scores*** An additional new analysis of MENSA was conducted to look at the SGRQ domains in the accepted population (analysis of covariance [ANCOVA] with covariates of treatment baseline, region and baseline percent predicted and FEV1). The frequency of respiratory symptoms domain was the key driver of the total SGRQ score (**Error! Reference source not found.**, Table 5). This provides further evidence supporting that add-on mepolizumab has a major effect on patients daily symptoms (-24.8 from baseline and -12.5 compared to placebo, 100mg SC). **Figure 2 Analysis of difference versus placebo in SGRQ score by domain versus placebo and from baseline (accepted sub-population, 100mg SC, MENSA)**	

Consultee	Comment [sic]	Response



Note: Analysis of MENSA performed using analysis of covariance (ANCOVA) with covariates of treatment baseline, region and baseline percent predicted FEV1

Table 5 Analysis of Change From Baseline in SGRQ Score by Domain (accepted sub-population, MENSA)

		Placebo	*100mg SC*	*75mg IV*
Activity domain	**n**	**64**	**91**	**74**
	LS Mean (SE)	50.9 (2.58)	45.2 (2.17)	45.3 (2.41)
	LS Mean Change (SE)	-9.1 (2.58)	-14.8 (2.17)	-14.7 (2.41)

Consultee	Comment [sic]	Response

	Diff vs placebo (95% CI)		**-5.8 (-12.4,0.9)**	**-5.6 (-12.6,1.4)**
Impact domain	**n**	**64**	**92**	**74**
	LS Mean (SE)	31.9 (2.07)	24.9 (1.74)	24.0 (1.94)
	LS Mean Change (SE)	-8.6 (2.07)	-15.6 (1.74)	-16.4 (1.94)
	Diff vs placebo (95% CI)		**-7.0 (-12.3,-1.7)**	**-7.8 (-13.5,-2.2)**
Symptom domain	**n**	**64**	**92**	**74**
	LS Mean (SE)	51.3 (2.89)	38.8 (2.41)	40.2 (2.70)
	LS Mean Change (SE)	-12.3 (2.89)	-24.8 (2.41)	-23.5 (2.70)
	Diff vs placebo (95% CI)		**-12.5 (-19.9,-5.1)**	**-11.2 (-19,-3.4)**

Note: Analysis of MENSA performed using analysis of covariance (ANCOVA) with covariates of treatment baseline, region and baseline percent predicted FEV1. Subjects with >=0.30 GI/L Blood Eosinophils at Baseline or Anytime in the Past 12 Months and either >=4 Exacerbations in Past Year or Maintenance OCS Use

1.2.2. Subject- and clinician-rated overall evaluation of response & other measures

A tertiary endpoint in both pivotal phase III trials (DREAM and MENSA) included a question while blinded to treatment to both the Investigator and subject, asking about their overall evaluation of treatment response. A 7-point scale was utilized ranging from significantly improved, moderately improved, mildly improved, no change, mild worsening, moderate worsening, significant worsening. In both studies, the odds ratio (OR) of reporting an improvement vs. standard of care plus placebo statistically significantly favoured mepolizumab across all doses. This simple question highlights

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>that both physicians and patients perceive an overall significant benefit of treatment with mepolizumab.

There are also numerical improvements in reduced rescue medication use, daily asthma symptom scores and number of night time awakenings. Asthma-related quality of life is a global measure of the impact of asthma. Single domain measures, such as these are less sensitive and relevant to measuring symptom improvement in this severe population with long-term use compared to composite measures, (1) e.g. SGRQ and ACQ. (For full results, see Appendix A).

In summary, data have been presented, including new analyses highlighting mepolizumab’s benefit on symptoms over and above the benefit received from reducing exacerbations. This provides additional evidence and aligns with the ERG’s report and the clinical community’s opinion, that add-on mepolizumab has a direct positive effect on HRQoL in addition to exacerbation reduction benefit.

We therefore ask the committee to reconsider its position (ACD section 4.23), and include the impact of symptom improvement, in addition to that of exacerbations.</td><td></td></tr>
<tr><td>GSK UK LTD</td><td>EQ-5D Preferred to SGRQ
<table><tr><th>• Assumption in ACD</th><th>• ACD2 preferred assumption</th><th>• Revised company base case</th><th>• Justification •</th></tr><tr><td>EQ-5D (ACD section 4.22)
Preferred to SGRQ</td><td>• ✓</td><td>• ✓</td><td>Recognise the committee’s preferences for direct EQ-5D. Baseline adjusted values presented</td></tr></table></td><td>The committee’s considerations about the application of the EQ-5D to value health related quality of life are outlined in the FAD. The committee ‘s considerations are outlined insection 4.18 of the FAD.</td></tr>
</table>

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<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>
In the original submission, EQ-5D data captured in DREAM was included in the economic model only as a sensitivity analysis; given the ceiling effects seen with this instrument the base case used EQ-5D values mapped from SGRQ captured in MENSA. However GSK acknowledges that the committee would prefer directly derived EQ-5D values from a trial (ACD section 4.22), and as such, the revised base case uses EQ-5D values captured from the Phase IIb DREAM trial.

Closer scrutiny of the direct EQ-5D data from DREAM revealed a difference in baseline values between the mepolizumab and SoC arm in the accepted population. Baseline EQ-5D values for SoC were higher (0.794) than those in the mepolizumab group (0.716). Thus while the between group difference throughout the trial were relatively small (0.005) the mepolizumab patients improved substantially (+0.081) from baseline while the SoC group decreased slightly (-0.002).

To account for this, baseline adjusted results were obtained using standard statistical methodology (least squares means) from a mixed model of repeated measures with covariates of treatment, age, visit, baseline and interaction between treatment and visit and visit and baseline. This model predicts placebo EQ-5D values of 0.765 for placebo and 0.804 in mepolizumab; giving a difference between placebo and mepolizumab of 0.039. This still provides a more conservative assumption than using the EQ-5D values mapped from the SGRQ data (0.07).

Table 6 Revised data inputs for EQ-5D to account for baseline imbalance, mean (SE), DREAM
<table>
<tr><th>Timepoint</th><th>SoC</th><th>Mepo 75mg IV</th></tr>
<tr><td colspan="3">Observed</td></tr>
<tr><td>Baseline</td><td>0.794 (0.024)</td><td>0.716 (0.034)</td></tr>
<tr><td>Post baseline</td><td>0.792 (0.026)</td><td>0.797 (0.023)</td></tr>
<tr><td>Diff between baseline and post baseline</td><td>-0.002</td><td>0.081</td></tr>
</table>
</td><td></td></tr>
</table>

Consultee	Comment [sic]	Response

Diff between SOC and mepo		0.005
Baseline-Adjusted		
Baseline	0.747	0.747
Post baseline	0.765 (0.020)	0.804 (0.020)
Diff between baseline and post baseline	0.018	0.057
Diff between SOC and mepo		0.039

**It should be noted that this difference in baseline levels of EQ-5D between the two groups is not reflected in other differences in baseline characteristics on the groups which are otherwise well matched (Table 5, Appendix B).*

Limitations of the EQ-5D

Whilst we use the EQ-5D in our revised company base case, there is good reason to believe that doing so leads to an overly conservative estimate of the health related quality of life (HRQoL) benefit of mepolizumab.

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, using a mapping equation, (2) the issue of this ceiling effect from the EQ-5D is addressed to some degree. 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, one third of patients reported perfect health on the EQ-5D at baseline despite their disease severity. However, nobody in MENSA scored a zero in SGRQ, i.e. nobody placed themselves in the best possible health state: as can be seen in Table 4, the minimum score was 5 in mepolizumab and 15 in the placebo arms. This was also the case in SIRIUS, where the minimum score was 8.

Consultee	Comment [sic]	Response
	In the one third of patients from DREAM who reported perfect health using the EQ-5D, it is not possible to capture any improvement in HRQoL. However, patients reporting 'perfect health' in EQ-5D can have less than perfect health as measured and picked up by the SGRQ. Mapping SGRQ to EQ5D may therefore help discriminate between patients with no apparent improvements in EQ-5D and help quantify the quality of life benefit (or decrement) perceived by these subjects which would otherwise be unobservable due to limitation of the EQ-5D-3L instrument (ceiling effect and a limited number of levels). For example, • If a subject were to report perfect health across two time points in the EQ-5D, there would be no improvement in quality of life observed from EQ-5D. • However, if this subject recorded a change in SGRQ at the same time points, the SGRQ (and mapping from it) can quantify this improvement (or decrement) which could not be observed through EQ-5D only: if the patient reported a change from 40.9 to 33.3 on the SGRQ, this would be interpreted as a 0.07 improvement in EQ-5D after mapping. • Thus, where 30% of the population has no change in EQ-5D, using the EQ-5D leads to a dilution of the treatment benefit at a population level Using SGRQ and the mapping of SGRQ to EQ-5D therefore helps quantify HRQoL in patients who apparently have no change in quality of life according to the EQ-5D, and thus a more representative HRQoL benefit at the population level. We recognise the committee's concerns with using SGRQ data mapped to EQ-5D, however we believe this does have some relevance to quantify the potential implication of the ceiling effect in EQ-5D and therefore it is presented as a sensitivity analysis. The 'most plausible ICER' is expected to lie between the baseline-adjusted direct EQ-5D and the mapped EQ-5D ICERs.	

Consultee	Comment [sic]	Response
GSK UK LTD	***Age adjusted utilities***	The committee's considerations about age adjusting utilities are outlined in section 4.19 of the FAD.

• Assumption in ACD	• ACD2 preferred assumption	• Revised company base case	• Justification •
• **Age adjusted utility (ACD section 4.23)** • Utility adjusts with age	• ✓	• **A**	Trial data shows that there is no evidence of utility being affected by age

In section 4.23 of the ACD, the committee considered that utilities should be age adjusted. It is understood that the ERG suggested that age adjusted utilities should be used in the analysis in order to ensure that nobody in the model states have a HRQoL greater than that observed in the general population (which in the model happens infrequently).

Whilst this adjustment has only a small effect on the ICER, it is a conservative adjustment applied by the committee. In order to assess its validity in the context of this model, the trial data were analysed by age to see if there were differences observed across different age bands, within the SoC arm.

Table 7 Analysis of age on EQ-5D, observed and baseline adjusted values in DREAM ITT, SoC group, mean (SE)

	Observed		Baseline Adjusted	
Age category	**Pre week 16**	**Post week 16**	**Pre week 16**	**Post week 16**
25-35	0.835 (0.061)	0.725 (0.131)	0.764 (0.032)	0.767 (0.026)
35-45	0.716 (0.084)	0.756 (0.092)	0.763 (0.028)	0.767(0.021)
45-55	0.807 (0.038)	0.791 (0.043)	0.763 (0.026)	0.766 (0.020)

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>
<table>
<tr><td>55-65</td><td>0.803 (0.037)</td><td>0.800 (0.044)</td><td>0.763 (0.028)</td><td>0.766 (0.022)</td></tr>
<tr><td>≥65</td><td>1 (n/a*)</td><td>0.922 (n/a*)</td><td>0.762 (0.033)</td><td>0.765 (0.026)</td></tr>
<tr><td colspan="5">*n=1 so no SE</td></tr>
</table>

As Table 7 shows, there was no difference observed between age and EQ-5D, across different age groups. As there is no evidence to support age adjusting utilities in this population, this assumption is not included in the company base case. Sensitivity analyses were however conducted to show the impact of including/excluding it from the base case, for completeness.
</td><td></td></tr>
<tr><td>GSK UK LTD</td><td>
Continuation criteria
<table>
<tr><th>• Assumption in ACD</th><th>• ACD2 preferred assumption</th><th>• Revised company base case</th><th>• Justification
•</th></tr>
<tr><td>Continuation Criteria: (ACD section 4.15)
• original
• 50% reduction
• 30% reduction</td><td>. R</td><td>✓</td><td>Reflects committee's preference for a continuation criteria linked to improvement</td></tr>
</table>

We note that

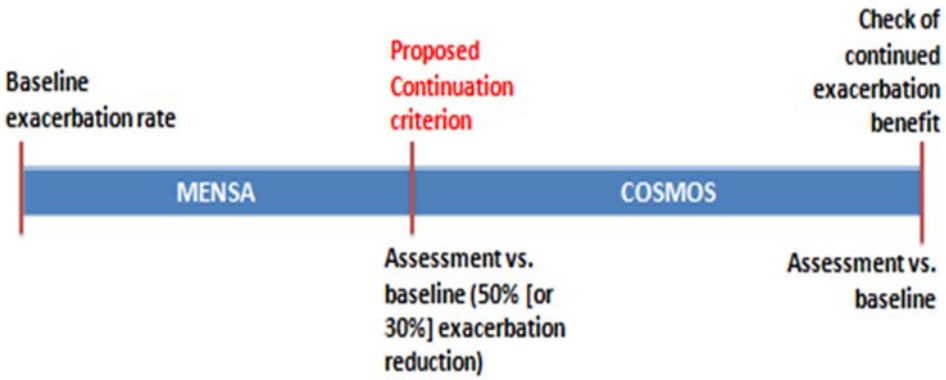
'the committee concluded that continuation criteria linked to improvement would have been more appropriate' (4.15).

This preference was supported by the severe asthma clinical community in their response to ACD1 as well as in our consultations with leading severe asthma specialists. The UK severe asthma clinical community have underlined their preference for a continuation criteria where mepolizumab is continued after 12 months if there has
</td><td>The committee's considerations about the inclusion of continuation criteria are outlined in the FAD. The committee agreed continuation criteria for the first year of treatment for its decision-making based on a reduction in exacerbation rate of 50% (see section 4.11 of the FAD).</td></tr>
</table>

Consultee	Comment [sic]	Response
	been a clinically meaningful reduction in exacerbation frequency or a reduction in maintenance OCS dose. To align with the committee's and clinical opinion, we therefore propose a continuation criteria that is more explicitly defined and consistent with the mepolizumab marketing authorisation, the clinical trial data, and clinical practice. ***1.6.1. Defining a continuation criteria based on improvement*** ***Clinically meaningful reduction in exacerbation rate*** *Original criterion* In our original submission we defined the continuation criterion as '*annualised exacerbation rate improves or remains the same at 12 months*'. We are including this in our revised base case, to enable the committee to consider the impact of the other aspects of our response. *50%* Severe asthma specialists, in their response to the first ACD, recommended that a 50% reduction in exacerbation rate should be applied as continuation criteria. Also in the phase IIb/III RCTs a 50% reduction in exacerbation rate was observed with mepolizumab treatment. Similar mean reductions were achieved for the more severe exacerbations requiring emergency department (ED) visit or hospitalisation. In order to align with the specialist community's preference for a continuation criteria with a 50% exacerbation reduction threshold at 12 months, we will present the relevant clinical and cost-effectiveness results. *30%* As previously outlined in the company submission (section 4.7), there is evidence that a 30% reduction in exacerbations represents a clinically meaningful benefit in patients with severe asthma who are uncontrolled on maximal SoC therapy (see Appendix C). This slightly lower threshold may allow for more clinical judgement to be applied in the context of other clinical factors such as improvement in their asthma control and quality	

Consultee	Comment [sic]	Response
	of life, whilst allowing more patients with frequent exacerbations to continue on treatment. We will therefore also present clinical and cost-effectiveness results for a continuation criteria requiring a 30% reduction in exacerbation rate at 12 months. ***Reduction in mOCS dose*** Whilst guidelines recommend reducing a patient's OCS dose to the lowest possible level, after discussions with severe asthma specialists, a clinically meaningful reduction in maintenance OCS dose is more difficult to define. This is dependent on local clinical practice as well as individual patient factors, such as baseline maintenance dose, co-morbidities and adrenal suppression. Thus, the rate and level of reduction in OCS dose defined as clinically meaningful will be different from patient to patient. Moreover, as discussed in the company submission and acknowledged by the committee, the current evidence base does not allow the economic model to include the clinical and cost-effectiveness to the NHS that would be seen from reducing patients' OCS exposure. We would therefore suggest a pragmatic OCS continuation criterion refined slightly from our original submission that will allow for individualised patient centred management, defined as: *a reduction in maintenance oral corticosteroid dose while maintaining asthma control*. In SIRIUS, in our accepted population, 66% achieved a reduction in mOCS dose while maintaining asthma control (100mg SC). Mepolizumab's licence states: *The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations* (as per SmPC section 4.2). In consideration of the license and the factors outlined above, best clinical practice and the severe asthma specialist community in the UK, we recommend the committee to consider a continuation criteria that will allow appropriate identification of patients with a clinically meaningful benefit from add-on mepolizumab treatment, and thus should be continued on this therapy. We propose the following wording for a continuation criteria:	

Consultee	Comment [sic]	Response
	• *Mepolizumab therapy should be continued if at 12 months from initiation of treatment:* – *A 50% (or 30%)* ***reduction in the number of exacerbations*** *is observed compared to the prior 12 months* *OR* – *A* ***reduction in maintenance oral corticosteroid dose*** *is observed while maintaining asthma control* ***1.6.2. Supporting Data for the Revised Continuation Criteria*** ***Analysis assessing the appropriateness of applying a continuation criterion based on an improvement of 50% (or 30%) in annual exacerbation rate, using 84 weeks of clinical trial data*** We are able to demonstrate the appropriateness of applying a continuation criterion based on reducing exacerbations by 50% (or 30%) using mepolizumab patient level trial data, which covered almost a 2 year period. Patients were treated on mepolizumab for 8 months in MENSA and continued for a further 12 months in the open label extention (OLE) study, COSMOS. • The continuation criterion was applied to the accepted sub-population on add-on mepolizumab treatment at the end of MENSA. Patients were categorised as 'met' if they had a 50% (or 30%) reduction in exacerbation rate at the end of MENSA compared to baseline, or 'not met' if they did not achieve that 50% (or 30%) reduction (i.e. 'met' = patients who would continue on treatment in the real world after 12 months and 'not met' = patients who would stop in the real world). • For the purpose of this analysis only, patients who both 'met' and 'not met' the continuation criterion at the end of MENSA were then assessed again at the end of COSMOS, and categorised as 'met' if they had a 50% (or 30%) reduction in exacerbation rate at the end of COSMOS compared to baseline before MENSA or 'not met' if the did not achieve that 50% (or 30%) reduction.	

Consultee	Comment [sic]	Response
	This methodology (further explained in Figure **3**) allows for an objective assessment of whether a 50% (or 30%) reduction in exacerbation rate acheived at 12 months is still maintained (or improved) in the following year. It also shows whether those patients that don't receive sufficient benefit in year 1 (end of MENSA) (and would therefore discontinute treatment in the real world), would go on to have received benefit in year 2 (end of COSMOS). The results of this analysis are shown in Table 8. **Figure 3 Methodology of percentage reduction in exacerbation continuation criteria analysis using MENSA and COSMOS data**  Although the duration of MENSA (8 months) was shorter than the proposed continuation criteria to be applied at 12 months, using the above methodology still informs on the validity of applying this continuation criteria, given it applies an annualised exacerbation rate. Additional points supporting the use of MENSA data to inform on a 12 month based continuation criteria are: • In DREAM, a 12 month exacerbation study, a consistent and similar reduction in exacerbations was observed: 48% with 75 mg IV at 12 months in DREAM	

Consultee	Comment [sic]	Response

compared to 47% with 75 mg IV (53% with 100 mg SC) at 8 months in MENSA.

- Treatment response with mepolizumab is only marginally affected by seasonal changes in exacerbation frequency [Ortega, 2014], thus the 8 months MENSA trial was deemed sufficient to inform of mepolizumab's effect on annual exacerbation rates.

- The regulators accepted the use of MENSA as a key licensing study and proposed a 12 month treatment review based on this evidence.

Table 8 Summary of subjects in the accepted subgroup treated with mepolizumab meeting and not meeting a 50% (or 30%) reduction in exacerbations in MENSA and COSMOS, compared to the baseline exacerbation rate the year prior to MENSA.

	MENSA		COSMOS	
Continuation criteria	**Met / not met percentage reduction in exacerbations at end of MENSA, n (% of total population, n=159)** ***(Continuation criteria)***		**Met / not met percentage reduction in exacerbations at end of COSMOS, n (% of total population, n=159)** ***(post continuation criteria)***	
			Met	**Not met**
≥50% reduction in exacerbation rate vs. baseline	Total n	159	121 (76)	38 (24)
	Met	122 (77)	103 (65)	19 (12)
	Not met	37 (23)	18 (11)	19 (12)
≥30% reduction in exacerbation rate vs. baseline	Total n	159	136 (86)	23 (14)
	Met	134(84)	124 (78)	10 (6)
	Not met	25 (16)	12 (8)	13 (8)

Percentages in rows and columns are in relation to the total number of subjects (N=159).

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>
Results for those meeting continuation criteria

Applying the continuation criteria to the accepted sub-population showed that after MENSA, 77% (122/159) achieved a 50% reduction and 84% [134/159] achieved a 30% reduction in exacerbation rate (Table 8).

Importantly, 65% (103/159) of patients in the accepted sub-population met the 50% continutation criteria in MENSA and continued to benefit in COSMOS (78% [124/159] continued to benefit for 30%) (Table 8).

Results for those not meeting continuation criteria

At the end of MENSA, 23% (37/159) did not achieve a 50% reduction in exacerbation rate and 16% [25/159] did not achieve 30% reduction.

12% (19/159) of patients in the accepted sub-population did not achieve a 50% reduction in exacerbations in both in MENSA and COSMOS (8% [13/159] did not achieve a 30% in MENSA and COSMOS) (Table 8).

Given there is some inevitable variation in asthma control, the results above give reassurance that a continuation criteria based on percentage reduction in exacerbations is a reasonable approach. Applying the 30% threshold has the benefit that the chance that you discontinue someone who has not yet received benefit, but may do so in the future, is lower than with the 50% rule. However with the 50% threshold the number of patients that discontinue but may have had benefit in the future is still low, and this level is more in line with the asthma specialists' views on a clinically meaningful reduction. Both criteria align with mepolizumab's licence, and are consistent with the committee's preference for a continuation criteria based on improvement.

1.6.3. Summary of proposed continuation criteria based on Guide to the Methods of Technology Appraisal 2013

<table>
<tr><th>Considerations for the continuation criteria (5.10.12 Guide to the methods of technology appraisal 2013)</th><th>GSK Considerations</th></tr>
</table>
</td><td></td></tr>
</table>

Consultee	Comment [sic]		Response
	...the robustness and plausibility of the end point on which the criteria is based	Exacerbations are cited as an appropriate basis for a continuation criterion in the SmPC. Given the specialist nature of severe asthma management there is a consistent understanding of what constitutes an asthma exacerbation. The criteria also include patients reducing oral steroid dose as this is a recognised alternative benefit of treatment.	
	...whether the 'response' criteria defined in the rule can be reasonably achieved	It was achieved in mepolizumab clinical trial data, for the accepted population in MENSA, showing that 77% of patients experienced a ≥50% reduction in exacerbations (84% of patients experienced a ≥30% reduction).	
	...the appropriateness and robustness of the time at which response is measured	The time-point is as recommended in the SmPC. The criterion is implemented using annualised exacerbation rates based on the MENSA trial. The EMA approved the license & recommended a 12 month review based on these data.	
	...whether the rule can be incorporated into routine clinical practice	Patients will be seen on a 4 weekly basis to receive treatment, and monitoring of exacerbations and steroid use would form part of a standard review of the patient's response to therapy. Therefore it can be easily incorporated into routine clinical practice.	
	...whether the rule is likely to predict those patients for whom the technology is particularly cost effective	The criterion improves cost-effectiveness and reflects the committee's preference for a continuation criterion based on improvement.	
	...considerations of fairness with regard to withdrawal of treatment from people whose condition does not respond to treatment.	The SmPC states, "The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations". The severe asthma	

Consultee	Comment [sic]		Response
		community have commented that a 50% reduction in exacerbations is a clinically appropriate level to review treatment. Whilst our analysis demonstrates that a few patients if allowed to continue may have received clinical benefit in the following year, they only represent a small proportion of the patient population. Given the nature of this variable heterogeneous disease any review is likely to have this implication and needs to be viewed in the context of balancing risk/benefit to patients when using a biologic.	

1.6.4. Implementing the revised continuation criterion in the economic model

The previous continuation criterion, of no worsening in exacerbation rate, was therefore revised to take into account the committee's preference that '*linked to improvement would have been more appropriate*' (ACD section 4.15). The same approach preferred by the committee for estimating exacerbation rates post continuation assessment were used, identifying patients meeting the criteria in MENSA and using COSMOS data for the exacerbation rates and the adjustments for SoC (ACD Section 4.19). In the context of the model inputs, new data were obtained for exacerbation rates, utilities and for the number of people meeting the continuation criteria, using a threshold of 50% (and a threshold of 30%). The model inputs are summarised in Table 10. The model inputs for the two continuation criteria were applied to the revised company base case and the results are presented in section 2.

Table 9 Model inputs, continuation criteria

Variable	Mean	SE	Source
Exacerbation parameters			
Patients meeting mepolizumab continuation criteria			

Consultee	Comment [sic]	Response

No reduction - exacerbations	Rate	1.020	0.114	COSMOS from MENSA
50% reduction	Rate	0.890	0.132	COSMOS from MENSA
30% reduction	Rate	1.020	0.124	COSMOS from MENSA
Not meeting continuation criteria				
No reduction - exacerbations	Rate	5.260	0.248	COSMOS from MENSA
50% reduction	Rate	3.270	0.182	COSMOS from MENSA
30% reduction	Rate	3.720	0.225	COSMOS from MENSA
% patients meeting mepo continuation criteria				
No reduction - exacerbations	p%	0.892	0.023	MENSA
50% reduction	p%	0.767	0.034	MENSA
30% reduction	p%	0.843	0.029	MENSA
Utility parameters				
Meeting Continuation criteria				
No reduction - exacerbations	Utility	0.806	0.023	DREAM
50% reduction	Utility	0.823	0.023	DREAM
30% reduction	Utility	0.824	0.023	DREAM

Rationale for not applying the mOCS part of the continuation criteria to the model

Because in MENSA, dosing of mOCS was optimised at baseline and patients were not allowed to reduce their dose during the trial, it was not possible to robustly apply the second part of the rule with the data that are available. We therefore applied the exacerbation-based criterion described above to the total accepted population.

1.6.5. Approach to Attrition

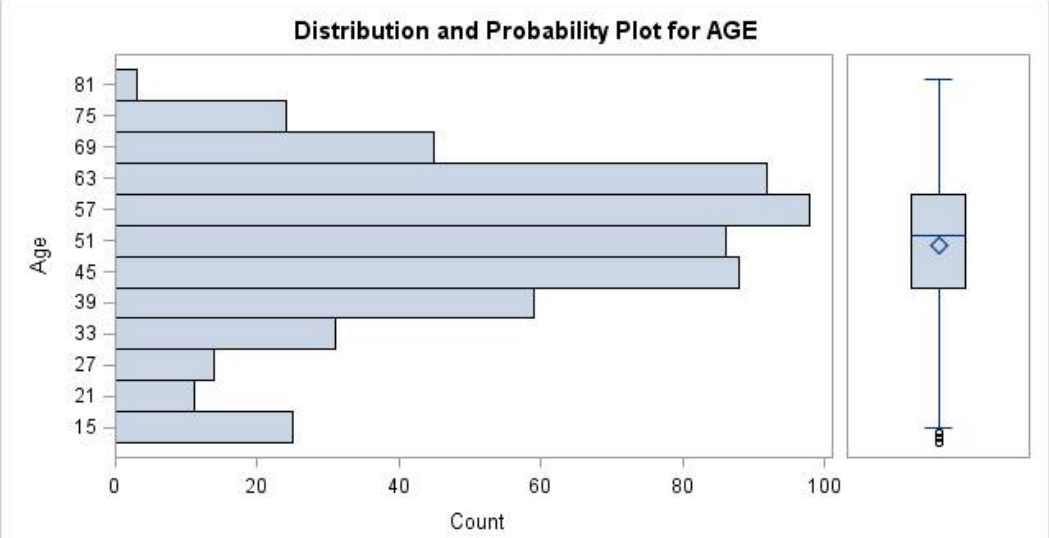
<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>In addition to the continuation criteria at 12 months on treatment, a 10% annual attrition rate is applied annually to the model from year 2 onwards. In section 4.15 the committee raised concerns that this figure seemed to be arbitrary. This figure was actually taken from our open label extension study COSMOS, which is likely to be reflective of long term clinical practice, where 10% of patients withdrew from treatment with mepolizumab (66/651). The ACD section 4.15 suggests assuming higher attrition rates would increase the ICER. Sensitivity analyses were previously conducted which adjusted the attrition rate and has shown that the ICERs remained relatively stable.

In summary, based on the information outlined above, we ask the committee to consider a continuation criteria that will allow appropriate identification of patients that receive clinically meaningful benefit from add-on mepolizumab treatment, to be continued on this therapy. Base case cost-effectivness results are provided in Section 2, showing the original continuation criterion, and exploring the impact of the 2 thresholds proposed.</td><td></td></tr>
<tr><td>GSK UK LTD</td><td>Age of eosinophilic asthma patients in the UK

<table><tr><th>Assumption in ACD</th><th>ACD2 preferred assumptions</th><th>Revised company base case</th><th>Justification</th></tr><tr><td>Age (ACD section 4.25)
Model start age of 50.1 years</td><td>R</td><td>✓</td><td>The committee noted that the impact on the ICER was marginal, so kept at 50.1</td></tr></table>
In the revised company base case, for the economic model, GSK have aligned with the ACD section 4.25 on age, and kept the starting age at 50.1 years.

The ACD does however suggest that age in the model (of 50.1 years) was likely to be older than that seen in clinical practice. However the proposed population for mepolizumab is a recognised phenotype, specifically late-onset eosinophilic disease. This is generally non-atopic, refractory to inhaled steroids and more likely to require</td><td>The committee’s considerations about the age of eosinophilic asthma patients in the UK are outlined in the FAD. The committee concluded that age of onset of treatment influenced the ICER and there was some uncertainty about the age of the ‘accepted’ population (see section 4.14 of the FAD).</td></tr>
</table>

Consultee	Comment [sic]	Response
	long term systemic corticosteroids. A BTS Registry study showed that late onset eosinophilic phenotype affects an older more established asthma population. People with late onset eosinophilic disease generally have had asthma for many years, but it is only when they are older that their asthma changes to be severe. When looking at a cohort of 245 people, late-onset, eosinophilic asthma was identified as a distinct category (n=32), with a mean (SD) age at baseline of 49 (14.6) years, and age at onset of symptoms was 34.5 (16.5) years (3). Note this compares with early-onset, atopic asthma (typically treated with omalizumab), with a mean age of 40.2 (13.7) years, with strikingly, an age at onset of symptoms of 10.2 (9.97) years (3). A more recent Thorax (2016) publication looking at two UK severe asthma populations, confirmed a mean age of 50 (14.5) years in 770 BTS registry patients (data collected from UK dedicated Specialist Difficult Asthma Services) and a mean patients age of 59 (17) in the Optimum Patient Care Research Database (n=808), a UK respiratory database containing anonymised primary care data (4). Given the cohort defined in the proposed population may be primarily late-onset, descriptive data from MENSA were generated to describe the distribution of age in the trial and so in this population (Figure 4). This cohort was seen to have a skewed distribution, such that the mean age of 50.1 years (as shown by the diamond in the plot), is younger than the median age of 52.0 years, which in turn is younger still than the modal age of 60.0 years. **Figure 4 Age distribution in MENSA**	

Consultee	Comment [sic]	Response
	 The new analyses on age-adjusted mortality, as described above, together with the demographics of people with late-onset eosinophilic asthma, indicate that this population are likely to be at an elevated risk of death from asthma mortality. As such, it is useful to also consider which average statistic of age we use to model this specific phenotype of the disease. To account for this skewed distribution, in a sensitivity analysis, we assessed the impact of using the median age of 52.0 years rather than the mean age of 50.1 years. In section 2 this shows that an increase in age to 52 years is associated with a small reduction in the ICER. Therefore we believe a starting age of 50.1 years in the model is reasonable, and is appropriate for use in the base case	
GSK UK LTD	***Consideration of waning of treatment effect*** In Section 4.26 the committee assumed a waning effect was likely to increase the ICER. However in our revised base case no change to the original model assumptions	The committee's considerations about the waning of treatment effect are outlined in the FAD. The committee's considerations about the inclusion of continuation criteria are outlined in

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>have been made. This assumption is supported by data from the COSMOS study (5), which showed that patients continue to benefit in terms of exacerbation rate, mOCS reduction and ACQ without a waning effect when continued on add-on mepolizumab treatment. Furthermore, as previously explained, 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 assumption of continued effectiveness was discussed at the committee meetings and was supported by the clinical experts present during the initial meeting. In addition, with more than 10 years of clinical experience in the UK using omalizumab, the only other biologic in severe asthma, there has been no evidence of potential waning with therapy. Therefore we believe in the absence of any evidence to the contrary, this should not be considered as an ongoing uncertainty in the analyses.</td><td>section 4.11), the committee considerations about the benefit lasting over the life time of the model is outlined in section 4.17 of the FAD.</td></tr>
<tr><td>GSK UK LTD</td><td>Accounting for reduction in maintenance OCS use
<table><tr><th>Assumption in ACD</th><th>ACD2 preferred assumptions</th><th>Revised company base case</th><th>Justification</th></tr><tr><td>mOCS benefit (ACD section 4.28)</td><td>R</td><td>✓</td><td>Tries to quantify the benefits of avoiding mOCS use. Included as variation to base case.</td></tr></table>
The committee acknowledged the significant adverse effects of oral corticosteroid use, and that this had not been fully captured in the QALY measure. We agree that the long-term health benefits of reducing OCS exposure are difficult to capture fully in the economic evaluation. This has been recognised as a challenge in NICE appraisals across a range of disease areas. Even small reductions in mOCS dose can potentially have significant benefit to patients. Patients on <5mg/day have much larger odds of developing associated complications (OR 2.50), with an almost doubling incidence rate ratios for inpatient visits (RR 1.86) (6).</td><td>The committee's considerations about the reduction of long-term systemic corticosteroids are outlined in the FAD. The committee acknowledged that there were adverse effects associated with the use of long-term systemic corticosteroids. The committee agreed that benefits related to minimising the significant adverse effects of systemic corticosteroid use had not been fully captured in the QALY measure and considered this when making its recommendation (see section 4.21 and 4.22 of the FAD).</td></tr>
</table>

Consultee	Comment [sic]	Response
	In considering how to quantify this benefit, we looked to the approach taken in TA278 (omalizumab), which modelled the costs and consequences of OCS in severe asthma, and which we can consider to have some relevance with respect to the potential scale of the impact. This analysis reduced the reported base case ICER by between £4,000 and £6,000 in two of the resulting published articles from the assessment (7;8), and by between £10,000 and £17,000 per QALY gained in the assessment report. (9) One of these values was adopted (subtracted from the pre mOCS ICER), to give the most plausible ICER for the omalizumab appraisal. From the detail contained within the FAD, it is not clear which, and so we present a reduction of £4,000-£9,000 to the ICER as an additional scenario to our base case analyses. Whilst we acknowledge this to be a crude estimate, this helps to quantify the potential impact of the mOCS sparing effect. Accounting for this treatment benefit would significantly improve the base case ICER.	
GSK UK LTD	***Comparison with omalizumab*** We acknowledge the change in the ACD which reflects the evidence that mepolizumab is effective in patients that have previously received omalizumab. However we remain concerned over the rejections of the comparison with omalizumab. In Section 4.10 the committee have decided not to consider the comparison between mepolizumab and omalizumab further due to uncertainty in the evidence (primarily resulting from the lack of availability to us of patient level data for omalizumab) and also because feedback from clinicians did not consider the comparison appropriate as few patients would be likely to have either drug. We agree that the overlap population that would be eligible for either mepolizumab and omalizumab is relatively small and that given the distinct phenotypes involved, patients would tend to be offered the treatment most appropriate to their presenting symptoms if both were available on the NHS. However if the current draft negative recommendation for mepolizumab by NICE is confirmed, this will not be the case as those patients more appropriate for mepolizumab would not be able to be prescribed this treatment. Therefore clinicians would have no option but to either prescribe omalizumab, or continue with SoC, which	The committee's considerations about the comparison with omalizumab are outlined in the FAD. The committee noted that that the company did not present any new evidence. The committee concluded that the results from the company's indirect comparison of mepolizumab with omalizumab were highly uncertain and not suitable for decision-making, and did not consider this comparison further (see section 4.9 of the FAD).

Consultee	Comment [sic]	Response
	is likely to involve an increased use of oral corticosteroids and their associated significant side-effects. As a result of this initial decision by the committee no further consideration has been made of the relative cost effectiveness evidence that has been provided (Section 4.13). We believe that in the context of draft negative guidance for mepolizumab it is important to also review this evidence including the impact of the updated PAS and the approach to uncertainty in the clinical evidence. In the analysis provided in our original submission utilising the original PAS price mepolizumab was dominant in most scenarios considered. In this response GSK has further improved the PAS price that is being offered and as a result mepolizumab is likely to be a cheaper option in all scenarios – even utilising the most conservative assumption on dose of omalizumab used in clinical practice (accuracy dependent on the confidential PAS price for omalizumab). We accept that there is some inevitable uncertainty in the estimates of relative effectiveness; however given the context that clinicians are likely to prescribe dependent on the presenting phenotype, we believe that the committee should consider providing guidance that will enable patients that meet the NICE criteria for omalizumab as well as mepolizumab to be able to be prescribed the most clinically appropriate option for them (and with mepolizumab at a cost saving to the NHS). An underlying driver of the positive guidance for omalizumab and the current draft negative recommendation for mepolizumab is the differences in approach to the assumptions underpinning the cost effectiveness analysis accepted as most plausible by the respective committees. Whilst we agree that these appraisals concern different types of asthma, and the evidence base is evolving, the evidence underpinning the assumptions is primarily driven from common sources and there is no reason to believe that these are any more or less relevant for eosinophilic than atopic asthma. In the NICE *Guide to Methods of Technology Appraisals 2013*, it states that as far as possible judgements should be consistently applied between appraisals. If the preferred assumptions taken from the omalizumab MTA were incorporated in the analysis for mepolizumab, it would result in a highly cost effective medicine that therefore would likely be subject to positive NICE guidance.	

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>In conclusion, we would therefore ask the committee to reconsider the comparative evidence in this context. To be clear, in proposing this we are not suggesting that mepolizumab should be made available in preference to omalizumab – only that in the overlap population clinicians should be able to prescribe the medicine that is most appropriate for people based on their phenotype as described in Section 4.10 of the ACD, given there would be no opportunity cost to the NHS of doing so.</td><td></td></tr>
<tr><td>GSK UK LTD</td><td>
Modeling the impact of the different model assumptions on cost effectiveness, and the revised company base case

As can be seen throughout this response, GSK has considered the committee's conclusions and concerns in ACD2, and has taken steps to generate new data, conduct further analyses, revise model inputs and offer a revised PAS to address these. The new elements, together with most of the adjustments to assumptions made by the committee, give a revised company base-case which is summarised in Table 10.

Table 10, Assumptions used in cost effectiveness model, ACD2 preferred and revised company base case (including revised PAS)

Key: ✓ = preferred and incorporated by committee / included in GSK base case
R = raised but not included in committee base case
A = not incorporated in GSK base case & alternative proposed

<table>
<tr><th>Assumption in ACD</th><th>ACD2 preferred assumption</th><th>Revised company base case</th><th>One way impact on the ICER from ACD2 preferred to revised company base case</th></tr>
<tr><td>Age
Model start age is 50.1</td><td>R</td><td>✓</td><td>N/A</td></tr>
<tr><td>Treatment duration
Lifetime</td><td>✓</td><td>✓</td><td>N/A</td></tr>
</table>
</td><td>The committee's considerations about the company's cost-effectiveness results in the 'accepted' population are detailed in the FAD. (see section 4.20 of the FAD).</td></tr>
</table>

Exacerbations rates **Source of exacerbation rates to be used post application of continuation criteria as per ERG proposals and committee's preference.**	✓	✓	N/A
Duration of exacerbation **Taken from MENSA relating to resource use**	✓	**A** ***Midpoint Lloyd-MENSA***	-£2,012
Effect on symptoms **No effect obtained on top of exacerbations**	✓	**A** ***Utilising Direct EQ-5D***	-£7,644
EQ-5D **Preferred to SGRQ**	✓	✓ ***Utilising Baseline Adjusted EQ-5D***	-£11,314*
Age adjusted utility **Utility adjusts with age**	✓	**A** ***No Utility Age Adjustment***	-£1,350
Age adjusted mortality **There is an impact of age on asthma mortality**	✓	✓ ***New Mortality Evidence***	+£1,164

* change in ICER reflects move from 'Utilising Direct EQ-5D' to 'Baseline Adjusted EQ-5D'

These revised assumptions were applied to an amended model (which combined the ERG's previous adjustments with those adjustments set out in the revised base case). On top of these analyses, the committee's preference for a continuation rule linked to improvement was applied. In addition, explicit quantification of the potential mOCS benefit of between £4,000-£9,000 reduction on the ICER was presented (Table 11).

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>
The analyses show that applying the revised company base case assumptions to the model for mepolizumab, together with the revised PAS, and the original continuation criteria gives a revised company base case ICER of £31,724 per QALY gained (Table 11).

When introducing a 50% continuation criteria, a base case ICER of £27,418 per QALY gained (Table 11) is obtained. Explicitly adding in benefits of mOCS as per TA278 reduction would bring the ICER down to between £18,418 and £23,418 per QALY gained. Applying a 30% continuation criterion leads to a slightly higher ICER of £28,398 per QALY gained, and between £19,398 and £24,398 when adding in an explicit mOCS benefit.

Table 11. Results of cost effectiveness analyses for revised company base case, with different continuation criteria (including revised PAS)
<table>
<tr><th>Results</th><th>Δ Costs (£)</th><th>Δ QALYs</th><th>ICER (£)</th></tr>
<tr><td>Original Continuation Criterion</td><td>[redacted]</td><td>[redacted]</td><td>31,724</td></tr>
<tr><td>Revised Continuation Criteria, 50% Reduction</td><td>[redacted]</td><td>[redacted]</td><td>27,418</td></tr>
<tr><td>Revised Continuation Criteria, 30% Reduction</td><td>[redacted]</td><td>[redacted]</td><td>28,398</td></tr>
<tr><th>Results</th><th colspan="2">Δ to ICER</th><th>ICER (£)</th></tr>
<tr><td>Revised Continuation Criteria, 50% Reduction, including mOCS benefit</td><td colspan="2">-£4,000-£9,000</td><td>18,418-23,418</td></tr>
<tr><td>Revised Continuation Criteria, 30% Reduction, including mOCS benefit</td><td colspan="2">-£4,000-£9,000</td><td>19,398 - 24,398</td></tr>
</table>
</td><td></td></tr>
<tr><td>GSK UK LTD</td><td>
Scenario analyses

1. Four scenario analyses are presented to explore the uncertainties around the ERG and the company base case, assuming the original continuation criteria, and a</td><td>The committee’s considerations about the company's cost-effectiveness results in the ‘accepted’ population are detailed in the FAD (see section 4.20 of the FAD).</td></tr>
</table>

Consultee	Comment [sic]	Response
	50% and 30% continuation criteria. The rationale and model inputs for each of these scenarios, have been explained and detailed in the relevant section of the response: 1. Using duration of exacerbations from MENSA rather than the midpoint of Lloyd and MENSA (see section 1.1) 2. Turning on the utility age adjustment, rather than being off (section 1.4) 3. Applying the EQ-5D mapped from SGRQ values, to indicate the potential scale of the ceiling effect (section 1.3) 4. Using the median age of the trial population (52 years), rather than the mean age (50.1 years) (section 1.7) The consultee submitted scenario analyses table 13, 14 and 15 in its response to consultation and have not been reproduced here. Please see Committee papers for the full response. The analyses show that adjusting for these uncertainties results in ICERs between **£21,275 and £28,134** (50% reduction in exacerbations) and **£23,193 and £29,828** (30% reduction in exacerbations), depending on the assumptions applied. Utilising duration of exacerbations from MENSA (scenario 1) and adjusting utilities for age (2) slightly increase the ICER, whereas applying the EQ-5D mapped from SGRQ (3) and the median age of the trial population (4) can be seen to improve the ICER. When applying the new continuation criteria, in all scenarios, the ICERs are still within the range which NICE may consider a cost effective use of NHS resources. In addition the committee has recognised that for this innovative medicine, there are elements of value that have not been well captured in the ICER. In particular, the significant benefit to patients of reducing oral steroid burden has not been included. We acknowledge that it is difficult to capture this in numerical terms. However, explicitly adding in benefits of mOCS as per TA278 reduction would bring the ICER down to between **£18,418 and £23,418 per QALY gained** (50% continuation criteria), and between **£19,398 and £24,398 per QALY gained** (30% continuation criteria). We	

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>acknowledge this is a relatively crude analysis, however it gives the committee an approximation of the scale of impact.

In addition, the potential benefits to carers have not been able to be quantified and could provide further improvement to cost effectiveness.

We therefore believe that mepolizumab in the accepted population, with a revised continuation criteria, provides a cost-effective use of NHS resources, and we ask the committee to reconsider its draft guidance.</td><td></td></tr>
<tr><td></td><td>Summary of factual inaccuracies

Factual inaccuracies to ACD1 were presented by the company in Table 10 and 12 of Section 2.4. Please find the corrected tables in the company response to ACD2

<table>
<tr><th>Description of inaccuracy</th><th>Description of proposed amendment</th><th>Justification for amendment</th></tr>
<tr><td>Section 3.10: “But, the injection-site reactions was higher for mepolizumab given subcutaneously (8%) than intravenously (1.7%).”</td><td>1.7% is incorrect. The sentence should therefore read, “But, the injection-site reactions was higher for mepolizumab given subcutaneously (8%) than intravenously (3%).”</td><td>Factual inaccuracy as the figure of 1.7% is incorrect. The percentage of injection-site reactions in the IV arm was actually 3%.</td></tr>
<tr><td>Section 3.28: Disutilities are written without a “-“ negative sign</td><td>Please add a “-“(negative sign), it should read -0.10 and -0.20.</td><td>Disutilities should be referred to with a ”–“ sign</td></tr>
<tr><td>Section 3.45 states that “14.5% of patients stopped oral corticosteroids</td><td>It is a misrepresentation to compare the 41.9% and 14.1% figures side by side and there is uncertainty as to</td><td>It is important to note that the 41.9% figure is not the proportion of ITT patients in EXALT who stop OCS.</td></tr>
</table></td><td>Comments noted. The FAD has been amended accordingly in response to the summary of technical comments/corrections on the ACD2.</td></tr>
</table>

Consultee	Comment [sic]			Response
	treatment in SIRIUS compared with 41.9% of those whose disease responded to omalizumab in the technology appraisal."	the extent of the steroid sparing effectiveness of omalizumab. We recommend to remove this statement.	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	

Consultee	Comment [sic]			Response
			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.	
	Section 3.48: Analysis 3 states, “patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year, and a blood eosinophil count of 300 cells/microlitre or more per year”.	Analysis 3 should state, “patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year, and a blood eosinophil count of 300 cells/microlitre or more in the previous year.	This re-wording just provides additional clarification on the proposed population.	
	Section 4.7: It states, “Having considered all the comments, the committee concluded that the population in analysis 3, that is, people with a blood eosinophil count of 300 cells/microlitre or more per year and at least one of the following...”	This sentence should be re-phrased to state, “Having considered all the comments, the committee concluded that the population in analysis 3, that is, people with a blood eosinophil count of 300 cells/microlitre or more in the previous year and at least one of the following...”	This re-wording just provides additional clarification on the proposed population.	

Consultee	Comment [sic]			Response
	Summary of appraisal, 4:10: “In addition, its guidance would not apply to asthma that has previously been treated with omalizumab because evidence for this position in the treatment pathway was not presented”. This is contradictory to what is stated in the Section 4.11.	In Section 4:11, it states “The company also presented further data from the MENSA trial stratified by prior omalizumab use, which showed that there is no evidence of differential effectiveness in people previously treated with omalizumab. The committee concluded that mepolizumab is effective in people previously treated with omalizumab”.	Our assumption is that the summary statement is incorrect and should be re-worded to that stated in 4.11.	
	Section 4.15: It states, “Also, the committee considered that a 10% attrition rate seemed to be arbitrary and did not constitute a formal continuation rule”	This sentence should be removed.	**1.** There are two reasons for this as the continuation rule and the attrition rate are two separate and distinct parts of the model: 2. i) In year 1, a continuation rule, of no worsening in exacerbation rates was applied, to the subpopulation in MENSA, which found that 89.2%, met the rule, and 10.9% did not meet the rule (applying the initially proposed continuation rule). This is a specific review and would only take place at 12 months. **3.** ii) The 10% annual attrition rate is applied to the model from year 2 onwards. This figure is estimated based on the clinical trial programme	

Consultee	Comment [sic]			Response
			for mepolizumab, specifically in the one year OLE study, COSMOS, where 10% of patients withdrew from treatment with mepolizumab (66/651). This assumption of attrition reflects that, consistent with good clinical practice, the ongoing need for treatment with mepolizumab will continue to be reviewed on the basis of risk benefit to the patients, as well as patient choice/non adherence. It is therefore not clear why the 10% attrition rate is regarded as arbitrary, and we suggest this statement be removed. 4. . Thus it has never been suggested that the attrition rate would constitute a formal continuation rule, and so this sentence should be removed as it is factually inaccurate.	

Below are some factual inaccuracies within Table 1 of Section 3.10. Corrected figures highlighted.

	Modified ITT population (95% CI)	Proposed population (95% CI)	Restricted population (95% CI)
MENSA (75mg IV)	0.53 (0.40 to 0.72)	0.40 (0.24 to 0.67)	0.39 (0.22 to 0.68)
MENSA (100mg SC)	0.47 (0.35 to 0.64)	0.50 (0.32 to 0.78)	0.39 (0.23 to 0.67)

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>
<table>
<tr><td>MENSA pooled (75mg IV and 100mg SC)</td><td>0.50 (0.39 to 0.65)</td><td>Not reported</td><td>Not reported</td></tr>
<tr><td>DREAM (75mg IV)</td><td>0.52 (0.39 to 0.69)</td><td>0.36 (0.24 to 0.55)</td><td>0.31 (0.18 to 0.53)</td></tr>
<tr><td>SIRIUS (100mg SC)</td><td>0.68 (0.47 to 0.99)</td><td>0.77 (0.51 to 1.17)</td><td>0.81 (0.40 to 1.64)</td></tr>
<tr><td>DREAM + MENSA (75mg IV or 100mg SC)</td><td>0.51 (0.42 to 0.62)</td><td>0.41 (0.31 to 0.55)</td><td>0.35 (0.25 to 0.50)</td></tr>
<tr><td>DREAM + MENSA + SIRIUS (75mg IV or 100mg SC)</td><td>Not possible</td><td>0.50 (0.40 to 0.64)</td><td>0.42 (0.30 to 0.57)</td></tr>
<tr><td colspan="4">Abbreviations: CI, confidence interval; ITT, intention to treat; IV, intravenous; SC, subcutaneous</td></tr>
</table>

The consultee submitted corrections to ACD1 in table 10 and 12 of section 2.4 and references in its response to consultation and have not been reproduced here. Please see Committee papers for the full response.

References
Appendices
The consultee submitted several appendices and references in its response to consultation and have not been reproduced here. Please see Committee papers for the full response.
</td><td></td></tr>
<tr><td>Asthma UK</td><td>1. Has all of the relevant evidence been taken into account?
Asthma UK considers mepolizumab to be a novel and innovative treatment that seeks to address an unmet need for people with severe eosinophilic asthma. While we appreciate that NICE has accepted some of the points we submitted in response to the first appraisal consultation document (ACD) around the target population for mepolizumab, some key considerations remain unaddressed and therefore many of</td><td>Thank you for your comments. After considering the comments received in response to the ACD2 in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD.</td></tr>
</table>

Consultee	Comment [sic]	Response
	the areas of concern are unchanged from our previous submissions – in particular around oral corticosteroid (OCS) use. The Committee heard from one patient expert on the serious reality of living with severe asthma. Another we have worked with describes their experience of the condition in clear terms: "On a bad day I feel like I'm drowning and I can't reach the surface of the water and I'm going to burst, yet a tiny, tiny bit of air keeps me alive. It's very scary – I feel like I'm living with a time bomb and if I have a bad attack I say to myself 'Is this the one that will kill me?'" 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 OCS, are often very serious. We were disappointed that a study by Sweeney et al. did not appear to be considered in relation to comorbidities resulting from severe asthma requiring systemic corticosteroid therapy (http://dx.doi.org/10.1136/thoraxjnl-2015-207630). This is a recent study, published online earlier this year, which presents data from two large severe asthma populations (the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry) and shows that OCS use results in a higher prevalence of comorbidities - including type II diabetes, hypertension and osteoporosis. The committee has again recognised that some benefits related to avoiding the significant adverse effects of OCS use had not been fully captured in the QALY measure (4.28). There is a significant gap in high quality data that considers the morbidity due to OCS use in people with severe asthma, but this should not mean that NICE cannot consider the evidence that is available. The Sweeney et al. paper has been described as "the best estimate yet of the burden of OCS treatment in severe asthma" (Choo & Pavord 2016, http://thorax.bmj.com/content/71/4/302.full). We were therefore disappointed that this was not included in the assessment of mepolizumab – this should be reconsidered by the committee and factored into the incremental cost-effectiveness ratio (ICER), in addition to quality-of-life benefits to carers. We note that this point was also made by both the manufacturer and British Thoracic Society in their responses to the ACD. Estimating the impact of the effects of OCS use is a crucial area that needs to be addressed, particularly given that from a patient perspective, reduced use is a key benefit of any future treatment. Mepolizumab is the first in what we anticipate will be a next generation of treatments for people with severe eosinophilic asthma. Unless the true impact of OCS use is captured, we are concerned that similar novel and innovative treatments for severe asthma will not be comprehensively assessed.	The committee's full considerations for each issues raised are outlined in section 4 of the FAD. The committee acknowledged that there were adverse effects associated with the use of long-term systemic corticosteroids. The committee agreed that benefits related to minimising the significant adverse effects of systemic corticosteroid use had not been fully captured in the QALY measure and considered this when making its recommendation (see section 4.21 and 4.22 of the FAD).

Consultee	Comment [sic]	Response
	One patient wrote to Asthma UK recently to give us an insight on how mepolizumab had improved their day-to-day life. His asthma meant that he would be totally out of breath after a short walk, light-headed, and gasping for breath. After taking part in one of the trials for mepolizumab in Southampton he was able to act as a sole carer to his wife over several years before her death – in his words, he "could not have done this without the aid of the drug." Every effort should be made to ensure this is made available to patients. Whilst this is only one example Asthma UK believes this brings to the fore the lived experience of severe asthma and the impact that it has on people's quality of life and the role that they are able to play in society through work and family life. Innovative new treatments that enable people to play a greater role, live more independently and enable people to do more through employment and in family life are urgently needed for this cohort.	
Asthma UK	**2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We note that the committee has remained unchanged on the issue of how to capture the health-related quality-of-life benefits of mepolizumab in its model. Clinicians we consulted as part of our response to the first ACD agreed that the St George's Respiratory Questionnaire (SGRQ) was a more appropriate method than EQ-5D for measuring improvements in quality of life for people with severe asthma due to it being able to effectively capture exacerbations. As highlighted by the manufacturer, in the DREAM study, a third of patients reported "perfect health" on the EQ-5D at baseline. Severe asthma is a condition where between attacks patients can be considered well in between exacerbations of their condition. However, quality of life is severely impaired during attacks and, in many patients with severe eosinophilic asthma, by the treatment required to treat and prevent these attacks. EQ-5D is effective in capturing some measures of patients' health-related quality of life, but often these are not key issues for people with severe asthma. In contrast, SGRQ focuses more on capturing the quality of life measures of primary concern to people with a severe respiratory condition - measuring symptom-control (such as cough, wheeze, breathlessness, frequency of attacks), activity (focusing on limitations due to breathlessness), and impact (which includes a range of factors including side effects of prescribed medication). Similarly we would not expect these factors of concern to people with severe asthma to be applicable to a number of non-respiratory conditions. NICE has to appreciate that in relying on EQ-5D measures it is missing the true impact this treatment has on severe asthma.	The committee's full considerations for each issues are outlined in section 4 of the FAD. The committee concluded that mepolizumab probably improves symptoms as well as reducing exacerbation rates (see section 4.19 of the FAD), the committee also considered the approach to utilities in section 4.18 of the FAD. NICE conducts appraisals in accordance with the National Institute for Health and Care Excellence (NICE): Guide to the methods of technology appraisal 2013. The reference case stipulates that the EQ-5D is the preferred method of assessing health related quality of life. The committee agreed with the company's approach to determining utility using the EQ-5D in the response to the second appraisal committee (see section 4.18 of the FAD). In its 3rd appraisal committee meeting, the committee noted the company used the ERG's preferred approach in its response to the second appraisal consultation document to estimate the asthma-related mortality and concluded that this was appropriate.

Consultee	Comment [sic]	Response
	We do not believe that “perfect health”, as captured in EQ-5D, is a true starting point for people with severe asthma, as they 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 – their baseline for what constitutes good health will naturally be set at a lower level for a condition they have had to manage throughout their lives. If the EQ-5D model is unable to capture improvements in quality of life in a third of the population modelled, this highlights the need for a more appropriate model. We urge NICE to reconsider using data from SGRQ in its model to help to fully capture the benefits from this treatment, which we believe are significant. For example, the MENSA study of mepolizumab showed that the baseline scores on the SGRQ in those with severe eosinophilic asthma were equivalent to those seen in patients with severe COPD (Ortega et al. 2014, http://www.nejm.org/doi/full/10.1056/NEJMoa1403290). Treatment with mepolizumab was associated with a 10 point improvement in SGRQ in the population accepted as being potentially eligible for treatment based on the latest ACD. The improvement in this measure is roughly 3 times more than has been found for Seretide vs placebo in severe COPD (Calverley et al. 2007, http://www.nejm.org/doi/full/10.1056/NEJMoa063070). We appreciate that the committee has considered two separate models on which to model age-related mortality. While Roberts et al. may look at a larger population and a broader range through its age stratification, it is likely to underestimate the number of deaths due to it not including comorbidities. In contrast, Watson et al. includes deaths from all causes after hospitalisation for asthma, so including this in the ICER model is more likely to capture mortality from comorbidities and give a more accurate picture of asthma mortality.	
Asthma UK	**3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Asthma UK remains deeply disappointed in the draft recommendation, and is extremely concerned that the ICER still fails to take key considerations into account relating to asthma. Mepolizumab is an innovative treatment which meets an unmet need for severe eosinophilic asthma and has shown significant clinical benefit in clinical trials. We strongly urge the appraisal committee to reconsider this draft decision. NICE must find a way to take into account the impact on improving the lives of carers, and the health and quality of life benefits of reducing OCS, which as highlighted by the appraisal committee would reduce the ICER.	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD. The committee concluded that mepolizumab probably improves symptoms as well as reducing exacerbation rates (see section 4.19 of the FAD).

Consultee	Comment [sic]	Response
Asthma UK	**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.	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD
NHS England	**Has all of the relevant evidence been taken into account?** No. The most recent publication examining treatment response to mepolizumab stratified by baseline eosinophil thresholds has not been included. Ortega et al. Lancet Respir Med 2016, epub.	Comment noted – after considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD.
NHS England	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The summary of clinical effectiveness is a reasonable interpretation of the evidence. The summary of cost effectiveness is an incomplete interpretation of the evidence. For instance: 4.17 – not responding to mepolizumab does not indicate more severe disease; 4.21 there is no evidence to support the hypothesis that there will be a weaning of treatment effect over time. Importantly the statements provided in 4.23 are incorrect. The committee are not justified in concluding that an on treatment utility gain was inappropriate given that in patients with a baseline blood eosinophil count of 300 mepolizumab produced a 10.4 point improvement in SGRQ and 0.49 improvement in ACQ-5. These symptomatic improvements cannot be explained solely on the basis of a decrease in exacerbation frequency. The committee should have modelled an appropriate stopping rule to examine its impact on the ICER per QALY.	The committee's full considerations for each issue raised is outlined in section 4 of the FAD. The committee concluded that mepolizumab probably improves symptoms as well as reducing exacerbation rates (see section 4.19 of the FAD) and accepted the companies approach to measuring utility in its response to the second appraisal (see section 4.18 of the FAD). NICE conducts appraisals in accordance with the National Institute for Health and Clinical Excellence (NICE): Guide to the methods of technology appraisal 2013. The reference case stipulates that the EQ-5D is the preferred method of assessing health related quality of life. The committee agreed with the company's approach to determining utility using the EQ-5D in the response to the second appraisal committee (see section 4.18 of the FAD). The committee concluded that mepolizumab probably improves symptoms as well as reducing

Consultee	Comment [sic]	Response
		exacerbation rates (see section 4.19 of the FAD). As indicated above the NICE committee does not conduct analyses – the NICE committee consider the companys evidence submission and the evidence review group critique of this submission. The committee asked the company to model continuation criteria at the second appraisal meeting. The committee agreed continuation criteria for the first year of treatment for its decision-making based on a reduction in exacerbation rate of 50%. Furthermore the committee concluded that specialist physicians should be trusted to assess the person's continuing response to treatment thereafter (see section 4.11 and 4.21 of the FAD).
NHS England	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No. The committee has not taken into account all of the evidence and has in part incorrectly interpreted the underlying pathophysiology of the disease when producing its modelling assumptions. Further work is required with regards both the addition of a stopping rule and the impact of the improvement in on treatment utility gain on the ICER per QALY.	The committee considered the evidence presented by the company and the evidence review group critique of this submission. After considering the comments received in response to the ACD2 in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Institute of Lung Health University of Leicester,	1. The document suggests that there needs to be a blood eosinophil count of ≥300 cell/microlitre in the previous year, but the term used is '≥300 cell/microlitre per year'. This is not a phrase generally used to describe a blood eosinophil count and will be confusing to physicians prescribing the medication. The phrase '≥300 cell/microlitre in the previous year (or previous 12 months)' is better.	Comment noted. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD

Nominating organisation	Comment [sic]	Response
Institute of Lung Health University of Leicester,	2. Exacerbations need to be qualified as 'severe exacerbations requiring a course of oral corticosteroids'	Comment noted. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD
Institute of Lung Health University of Leicester,	3. It is important that objective evidence of adherence/compliance is emphasised in the guidance	Comment noted. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD
Institute of Lung Health University of Leicester,	A further minor point not relevant to the description of the preferred population is that the guidance states on page 27 that the clinical experts could not offer a specific definition of the term refractory asthma. In fact we did offer such a definition taken from a consensus paper produced by the American Thoracic Society (1). It is just that this is not routinely used in clinical practice. 1. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. Am J Respir Crit Care Med. 2000;162(6):2341-51.	Comment noted. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD

Comments received from commentators

Commentator	Comment [sic]	Response
Novartis	1. Novartis believes that information regarding oral corticosteroid use should reflect the data that was presented for analysis and discussed at the committee meeting (changes in italic and underlined, section 4.7, page 30). Additionally, we believe the term 'maintenance' oral corticosteroid is ambiguous and subject to interpretation and greater clarity should be provided. **The current text states:** The committee noted that the company presented new analyses for 3 further populations after consultation (see section 3.48), with analysis 3 put forward as the company's preferred population. The committee noted that this included patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year, and a blood eosinophil count of 300 cells/microlitre or more per year. Having considered all the comments, the committee concluded that the population in analysis 3, that is, people with a blood eosinophil count of 300 cells/microlitre or more per year and at least one of the following: • 4 or more exacerbations in the previous year • on maintenance oral corticosteroids would best reflect the population seen in UK clinical practice. However, analysis 3 that was presented at the 2nd Appraisal Committee meeting included patients with an eosinophil count of 300 cells/microlitre in the last year AND continuous or frequent (≥4) treatment with oral corticosteroids in the last year. Therefore, we believe that this section should reflect the population included in the analysis and highlight the following suggested amends (italics and underlined): The committee noted that the company presented new analyses for 3 further populations after consultation (see section 3.48), with analysis 3 put forward as the company's preferred population. The committee noted that this included patients on *continuous or frequent* oral corticosteroids and/or 4 or more exacerbations in the previous year, and a blood eosinophil count of 300cells/microlitre or more per year. Having considered all the	Comment noted. The rationale for the 'accepted' population is discussed in section 4.4 of the FAD. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD

Commentator	Comment [sic]	Response
	comments, the committee concluded that the population in analysis 3, that is, people with a blood eosinophil count of 300 cells/microlitre or more per year and at least one of the following: • 4 or more exacerbations in the previous year • on *continuous or frequent (≥4) courses* of oral corticosteroids *in the previous year* would best reflect the population seen in UK clinical practice.	
Novartis	2. The following statement should be corrected to state omalizumab instead of mepolizumab (italics and underlined, section 4.11, pg 32) During its first meeting, the committee noted that the company had presented no data for using mepolizumab after omalizumab. After consultation, the company clarified that a small number of patients in the MENSA trial were previously treated with *omalizumab* (with an interval of 130 days) and that the efficacy was comparable to omalizumab-naïve patients in the subcutaneous 100-mg group.	Comment noted. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD

Comments received from members of the public

Role*	Section	Comment [sic]	Response
NHS Professional, Consultant Respiratory Physician	-	As clinicians looking after patients with severe asthma in the UK, we would like to comment on this NICE ACD. We are pleased that the committee is persuaded of the clinical effectiveness of this first in class novel therapy for patients with severe eosinophilic asthma. Once again we strongly disagree with the draft recommendation that mepolizumab is not recommended as an add-on for treating severe refractory eosinophilic asthma. There are consistent flaws within the committee's assumptions that are based on an incomplete understanding of both the underlying pathology and clinical reality of patients with severe asthma. We would strongly recommend that the committee seeks external expert input at their next meeting.	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
NHS Professional, Consultant Respiratory Physician		Cost effectiveness The proposed population of patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year with a blood eosinophil count of 300 cells/microlitre in the previous 12 months is logical and consistent with the patient population that we would wish to treat. 3.50 " Not including a utility gain for treatment with mepolizumab over and above the gain from a reduction in exacerbations is illogical. Ortega et al, Lancet Resp Med 2016, epub clearly demonstrates an improvement in patients with eosinophils of 300 or higher of 10.4 in SGRQ and 0.49 in ACQ-5. It is highly unlikely that a 59% reduction in annual exacerbation rate produces such a significant effect in these two patient reported outcome measures. Clearly the addition of a stopping rule would have a significant impact on the ICER per QALY. Based on the available evidence and expert clinical opinion we would suggest that mepolizumab is continued after 12 months if there has been a 50% reduction in exacerbation frequency and/or a 50% reduction in oral corticosteroid dose.	Thank you for your comments – which have been noted. The committee has addressed the issues raised in sections 4.11 and 4.19 of the FAD.
NHS Professional, Consultant Respiratory Physician		Committee discussion 4.17 The concept that patients who do not respond to mepolizumab are more likely to have severe disease than patients who do respond has no immunological or clinical plausibility and should be removed. Patients with T2 high driven inflammation may be IL-5 or IL-13 predominant and it does not follow that a lack of response to blocking a single pathway indicates increased disease severity. 4.18 For the reasons stated above the ERG's analysis is not more plausible. 4.21 There is no reason to suspect a waning of treatment effect. Patients have been successfully treated with omalizumab for over 10 years with no waning of the effect. 4.22 The unlicensed dose of mepolizumab used in DREAM was 75mg intravenously.	Thank you for your comments – which have been noted. The committee has addressed the issues raised in sections 4.6, 4.16, and 4.17 of the FAD.
NHS Professional, Consultant Respiratory Physician		Conclusion We agree that the currently defined patient population is the correct one to be applied to clinical practice and have included a stopping rule that we would be happy to apply to our carefully selected patient cohorts. We are concerned that incorrect assumptions made by the ERG are inflating the ICER per QALY and urge the committee to invite experts in severe asthma to attend the third appraisal committee meeting to help interpret the evidence base correctly.	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD.

Role*	Section	Comment [sic]	Response
Carer		I am writing this email to you in hope that it will get to the correct department that deals with the above new drug for severe asthma. Please could some one explain to me why you do the trials in England giving hope to hundreds of people then take away that one last hope by making it just out of reach . My daughter Jenny has been asthmatic since the age of eleven and has spent over half of her life in and out of hospital with eosinophilic asthma that is as yet been treatable with anything other than the standard asthma medication . In 2011 she was asked to participate into mepolizumab trial and she was lucky enough to have been on the middle dose and not a placebo . And for the time in 20 years this drug actually helped her and for that 12 months of the trial she didn't have one episode of exacerbation of her asthma and finally felt that there was hope for her to have some kind of near normal life , that now has been taken away because the nice has recommended that it is not used on the nhs . I would just like to point out that all the medication that my daughter is on at the moment (2 steroid inhaler 500mg 2 puffs twice a day 1 ventolin inhaler 2 - 8 puffs every 4 - 6 hours 1 atrovent inhaler 2 puffs 3 times a day a base dose of 10mg of prednisone daily only the last 3 months that has gone up to 50mg and is at present 25mg daily 2 tablets of 250mg of aminophyline twice a day and at least one visit to a&e a week some times 2 visits the cost of all of this per year far out weighs the cost for her to have the mepolizumab injection once a month . Why is it not available in the uk but is available in the US and the European Union . I would be grateful if some one could explain this to me . Thank you for taking the time to read this and I hopefully look forward to hearing from you .	Thank you for your comment. After considering the comments received in response to the ACD in conjunction with the new evidence submitted by the company, the committee recommended mepolizumab as specified in section 1 of the FAD.

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

Company response to the second ACD

5th August 2016

Executive summary

GSK appreciates the opportunity to respond to the second ACD (ACD2) and to submit additional evidence for discussion at the next appraisal committee meeting (ACM), which we believe will address uncertainties and questions raised by the committee.

Whilst we are disappointed that negative interim guidance has been issued for mepolizumab for a second time, GSK is reassured by the agreement of an appropriate population for guidance (henceforth referred to as the 'accepted population': ≥300 cells/μLin the previous year and 4 or more exacerbations in the previous year or on maintenance OCS), and that NICE has recognised the:

- Substantial morbidity in the severe eosinophilic asthma population and the need for alternative treatments (ACD Section 4.1)
- Clinical efficacy of mepolizumab at reducing clinically significant exacerbations (ACD Section 4.9)
- Degree of innovation and benefits not reflected in the ICER: the reduction in dependency on oral corticosteroid use and potential benefits to carers provided by this medicine (ACD Section 4.28).

It is anticipated that mepolizumab would be appropriate and available to only a relatively small number of severe asthma patients, already under the care of a specialist asthma centre. At present there are very limited treatment options for these patients and they remain at risk of frequent but unpredictable asthma attacks (exacerbations) that can lead to recurrent unscheduled hospital attendances, admissions and/or death.

GSK has considered the committee's conclusions and concerns in ACD2, and taken steps to generate new data, conduct further analyses, revise model inputs and offer an improved PAS to address the outstanding concerns. These new elements, together with most of the adjustments to assumptions made by the committee, give a revised company base-case, detailed in this response and summarised below.

Summary of the key new elements introduced

- The committee concluded that mepolizumab did not demonstrate benefit beyond that provided by the reduction in exacerbations (Section 4.23). GSK strongly refute this conclusion and in our response we provide new analyses, alongside existing data, which demonstrates the **health related quality of life (HRQoL)** and **symptom benefit** of mepolizumab. In addition, the benefits of mepolizumab beyond exacerbation reduction were supported by asthma experts in the clinical community in their response to the previous ACD. We therefore ask the committee to reconsider its position and accept mepolizumab is associated with an impact on HRQoL and symptoms over and above a reduction in exacerbations, and that this benefit should be included when determining the committee's most plausible ICER.

- Recognising the committee's preference to use directly derived **EQ-5D** values from the Phase IIb DREAM study rather than mapped EQ-5D from SGRQ values within the Phase III MENSA trial (section 4.22), our revised base case uses the directly derived

data; the data are adjusted for differences in EQ-5D at baseline in the agreed sub-group between the add-on mepolizumab and SoC arms.

- To respond to the committee's preference of stratifying **asthma-related mortality** into narrower age bands, a retrospective data analysis was conducted, with analyses by age band (section 4.24), including for those over the age of 45. This analysis confirmed the committee's view that there is increasing asthma mortality over the age of 45 years and has been included in our updated base case.

- In line with the committee's preference for a **continuation criteria** based on improvement (section 4.15) and clinician feedback in response to the first ACD, a more explicitly defined continuation criteria has been proposed, consistent with the mepolizumab license and clinical trial data. We propose two alternative exacerbation reduction thresholds for the committee to consider; 50% which is suggested by severe asthma clinicians, or 30% which is aligned to the available literature on a clinically meaningful reduction in exacerbations. The proposed wording for the criteria is:

  - *Mepolizumab therapy should be continued if at 12 months from initiation of treatment :*
    - *A 50% (or 30%)* ***reduction in the number of exacerbations*** *is observed compared to the prior 12 months*
      OR
    - *A* ***reduction in maintenance oral corticosteroid dose*** *is observed while maintaining asthma control*

- Whilst GSK considers that the initial **PAS** price offered was fair and represented good value for money to the NHS, in order to improve the cost-effectiveness further, an improved PAS has been submitted by GSK.

Based on the new data and analyses provided, the original continuation criterion and new PAS, the ICER is **£31,724 per QALY gained**. With the revised continuation criteria at 50% exacerbation reduction, the base case ICER is **£27,418 per QALY gained.** Using a 30% exacerbation reduction for the continuation criteria, the ICER would slightly increase to **£28,398 per QALY** gained. Accounting for the additional steroid-sparing benefits of mepolizumab not fully captured in the model (and recognised as critical by clinicians in their treatment decisions) could reduce the ICER further by £4,000-£9,000, using results previously applied in omalizumab appraisal TA278.

GSK is concerned that mepolizumab is not being considered as an alternative to omalizumab in patients eligible for both medicines (Section 4.10). In the small overlap population clinicians should be able to prescribe the medicine that is most appropriate for people based on their phenotype as described in the ACD – if final guidance remains negative this would not be the case. Allowing mepolizumab as an alternative to omalizumab would have no opportunity cost to the NHS, as with the revised PAS mepolizumab is likely to be a cost saving option. This should be considered in the context that the assumptions applied to the mepolizumab appraisal are more conservative than those used in the omalizumab appraisal (TA278). Applying the TA278 assumptions to mepolizumab improves its cost effectiveness.

The response that follows provides more detail on the revised company base case, data inputs used, and the corresponding results. We hope that with the provision of these additional analyses and the revised PAS price, the committee will recognise the value of mepolizumab to patients in England and Wales by issuing a positive recommendation for this small subgroup of severe asthma patients.

Has all the relevant evidence been taken into account? Are the recommendations sound and a suitable basis for guidance to the NHS?

After carefully considering the second ACD, we provide our responses together with new data, which results in a revised company base case incorporating the updated PAS. Overall, there is mutual agreement for nearly all elements and a brief rationale is provided where variance exists. Section 1 follows and sets out the details supporting the rationale for the revised company base case. Section 2 presents the cost effectiveness results utilising the new base case assumptions.

Table 1 Revised company base case

Key: ✓ = preferred and incorporated by committee / included in GSK base case
R = raised but not included in committee base case
A = not incorporated in GSK base case & alternative proposed

Assumption in ACD	ACD2 preferred assumption	Revised company base case	i) Justification ii) Section in response
Patient population (ACD section 4.7 & 4.13) people with a blood eosinophil count of ≥300cells/μL in the previous year and at least one of the following: • 4 or more exacerbations in the previous year • on maintenance oral corticosteroids	✓	✓	i) Agree ii) N/A
Treatment duration (ACD section 4.20) Lifetime	✓	✓	i) There is uncertainty on treatment duration in this chronic condition ii) N/A
Exacerbations rates (ACD section 4.16-4.19) Source of exacerbation rates to be used post application of continuation criteria as per ERG proposals and committee's preference.	✓	✓	i) Revised company base case utilises ERG approach preferred by the committee is considered reasonable ii) N/A
Duration of an exacerbation (ACD section 4.23) Taken from MENSA relates to the timing of resource utilisation	✓	**A**	i) ERG and company believe that in reality the duration will be somewhere between Lloyd and MENSA, so propose midpoint ii) Section 1.1
Effect on symptoms (ACD section 4.23) No effect obtained on top of exacerbations	✓	**A**	i) Company disagrees. Data show that there is an impact on symptoms ii) Section 1.2
Directly Elicited EQ-5D (ACD section 4.22) Preferred to SGRQ	✓	✓	i) Recognise the committee's preferences for direct EQ-5D. Baseline adjusted values presented ii) Section 1.3
Age adjusted utility (ACD section 4.23) Utility adjusts with age	✓	**A**	i) Trial data show that there is no evidence of utility being affected by age ii) Section 1.4
Age adjusted mortality (ACD section 4.24) There is an impact of age on asthma related mortality	✓	✓	i) New data shows that there is an impact of age on asthma mortality

			ii) Section 1.5
Age (ACD section 4.25) Model start age of 50.1years	**R**	✓	i) The committee noted that the impact on the ICER was marginal, so maintained at 50.1 ii) Section 1.7

Continuation Criteria: (ACD section 4.15) • **original** • **50%** • **30%**	**R**	✓	i) Reflects the committee's preference for a continuation criteria linked to improvement ii) Section 1.6
mOCS benefit (ACD section 4.28)	**R**	✓	i) Tries to quantify the benefits of avoiding mOCS use. Included as a separate scenario to base case. ii) Section 1.7

1 Rationale for the Revised Company Base Case

1.1 *Duration of exacerbations*

Assumption in ACD	ACD2 preferred assumption	Revised company base case	Justification
Duration of exacerbation (ACD section 4.16-4.19) Taken from MENSA; relates to the timing of resource utilisation	✓	**A**	ERG and company believe that in reality the duration will be somewhere between Lloyd and MENSA, so propose midpoint

In ACD section 4.23, it states that the ERG suggests incorporating the average length of exacerbations as measured in the MENSA trial, and that the committee considered this appropriate. However, this conclusion did not fully reflect our understanding of the ERG report and discussion at the committee meeting.

In its critique of the company's response to the first ACD (ACD1), the ERG acknowledged that there is potential for the utility to be underestimated using only the average length of exacerbations in MENSA, as this duration was defined by increased OCS use and not the time period during which HRQoL would be impaired. The company response to ACD1 explained that this is because there would be a tail end of the exacerbation once healthcare resource utilisation had ceased, when the utility decrement continued for longer, giving a censored duration of an exacerbation. The ERG considered that applying a 28-day period of disutility (as per Lloyd) and originally recommended by GSK, would overestimate the loss in utility if the impact on utility was assumed to be related to the key event. The ERG considered that

'it is plausible that the true disutility could lie between the estimates produced by the two approaches' (ERG critique of company response to ACD1, page 19).

This issue was discussed at the second Appraisal Committee Meeting (ACM2) where both the ERG and GSK proposed that the duration could feasibly be between MENSA and Lloyd.

In response to the comments by the ERG and the discussions in ACM2 that the duration of an exacerbation could be between the two sources, in the revised company base case, the model uses the midpoint between MENSA and Lloyd for the duration of exacerbations, as set out in Table 2.

Table 2 Duration of exacerbations (days) and midpoint used in revised company base case

Type of exacerbation	MENSA	Lloyd	Midpoint – revised company base case
OCS burst	12.7	28	20.3
ED visit	10.4	28	19.2
Hospitalisation	20.7	28	24.4

This revised assumption for the duration of an exacerbation, which utilises a midpoint between two sources, remains a conservative assumption relative to that used in omalizumab (TA278). Here the source of duration of an exacerbation was changed from the trial duration to Lloyd by the Assessment Group, the opposite of what is proposed by the committee here.

We therefore believe that taking the midpoint is a pragmatic approach and may still be a conservative estimate.

1.2 *Effect on symptoms*

Assumption in ACD	ACD2 preferred assumption	Revised company base case	Justification
Effect on symptoms No effect obtained on top of exacerbations	✓	**A**	Data show that there is an impact on symptoms

Section 4.23 of the ACD mentions that:

'the committee heard from the clinical experts that mepolizumab was unlikely to have an effect on symptoms. That the company disagreed, but was unable to provide any evidence that mepolizumab is associated with an impact on symptoms over and above a reduction in exacerbations. The committee concluded that an on-treatment utility gain was inappropriate'.

GSK strongly refute this conclusion; both the ERG at ACM2 and the feedback to ACD1 from severe asthma experts support that mepolizumab has a benefit on symptoms beyond exacerbation reduction:

- In its report, the ERG explains the data set out by GSK, which shows a difference between mepolizumab and standard of care in SGRQ and ACQ-5, and explains that the model states are informed by analyses of patient level HRQoL data from the trials. Further the ERG explains that these data were the reason why the ERG applied differential utilities within the ERG base case in its report.

- Experts who responded to ACD1 (including those in the severe asthma clinical community from the 10 severe asthma BTS centres), clearly stated that mepolizumab has a symptom benefit, and challenges the committee's view that there is no evidence to support benefit of mepolizumab beyond that experienced from an improvment in exacerbation rate. This is consistent with feedback we received from clinicians who treated patients as part of the mepolizumab clinical trial programme.

Notwithstanding that mepolizumab has been acknowledged as being very effective at reducing clinically significant exacerbations, it is highly unlikely that this in isolation would cause the clinically meaningful size of improvement seen in the ACQ and the SGRQ and non-specific question to both physician and subjects about their impression of the overall evaluation of treatment response. This is supported by mepolizumab's mechanism of action as an anti-IL5 treatment, reducing eosinophilic inflammation. As presented in the company submission, by reducing the inflammatory aspects of asthma, mepolizumab improved symptom control, quality of life and lung function, in addition to reducing the risk of clinically significant exacerbations in the clinical trials.

To further demonstrate the benefit of mepolizumab on top of exacerbations, below we present:

- ACQ and SGRQ data with new analyses on SGRQ data showing the benefit of mepolizumab therapy over and above the benefit experienced from a reduction in exacerbations
- Subject- and clinician-rated overall evaluation of response & other measures

1.2.1. SGRQ and ACQ Data & Analyses

The St George's Respiratory Questionaire (SGRQ) has three domains (listed below) and the minimal clinically important difference (MCID) is 4 points.

1. frequency of respiratory symptoms
2. daily physical activity score
3. measuring impact on daily life

The ACQ-5 questionnaire asks about the symptoms listed below, and a change or difference in score of 0.5 is considered to be the MCID.

1. woken at night by symptoms
2. wake in the mornings with symptoms
3. limitation of daily activities
4. shortness of breath
5. wheeze

ACQ and SGRQ total score: existing HRQoL data

As previously presented for MENSA, the accepted sub-population had a significant disease burden at baseline with an ACQ-5 score of 2.3 (>1.5 is considered to be inadequately controlled asthma and an SGRQ score of 49.9 (100mgSC/75mgIV) (Table 3), despite being optimised on high dose asthma therapy. Mepolizumab was able to demonstrate a clinically

and statistically significant benefit in quality of life (SGRQ) and asthma control (ACQ) greatly above the MCID of 4 and 0.5, respectively, from baseline and versus placebo (Table 4).

Table 3 Baseline ACQ-5 and SGRQ scores, for accepted population, MENSA

		Placebo	Mepo 75mg IV/100mg SC
Baseline ACQ-5 Mean Score	N	68	171
	Mean (SD)	**2.5 (1.30)**	**2.3 (1.25)**
	Median (Min, Max)	2.5 (0, 6)	2.4 (0, 5)
Baseline SGRQ Total Score	N	68	174
	Mean (SD)	**51.7 (19.46)**	**49.9 (18.41)**
	Median (Min, Max)	52.6 (15, 95)	51.3 (5, 90)

Table 4 Change in ACQ-5 and SGRQ scores at 32 weeks, for accepted population, MENSA

		Placebo	Mepo 100mg SC	Mepo 75mg IV
ACQ	N	62	88	69
	LS Mean (SE)	1.97 (0.114)	1.32 (0.097)	1.4 (0.108)
	LS Mean Change (SE)	**-0.37 (0.114)**	**-1.02 (0.097)**	**-0.94 (0.108)**
Comparison vs placebo	**Difference**		**-0.65**	**-0.57**
	95% CI		-0.95, -0.36	-0.88, -0.26
	p value		<0.001	<0.001
SGRQ	N	64	91	73
	LS Mean (SE)	40.9 (2.04)	33.2 (1.71)	33.3 (1.92)
	LS Mean Change (SE)	**-9.4 (2.04)**	**-17.1 (1.71)**	**-17.0 (1.92)**
Comparison vs placebo	**Difference**		**-7.7**	**-7.6**
	95% CI		-13, -2.5	-13.2, -2.1
	p value		0.004	0.007

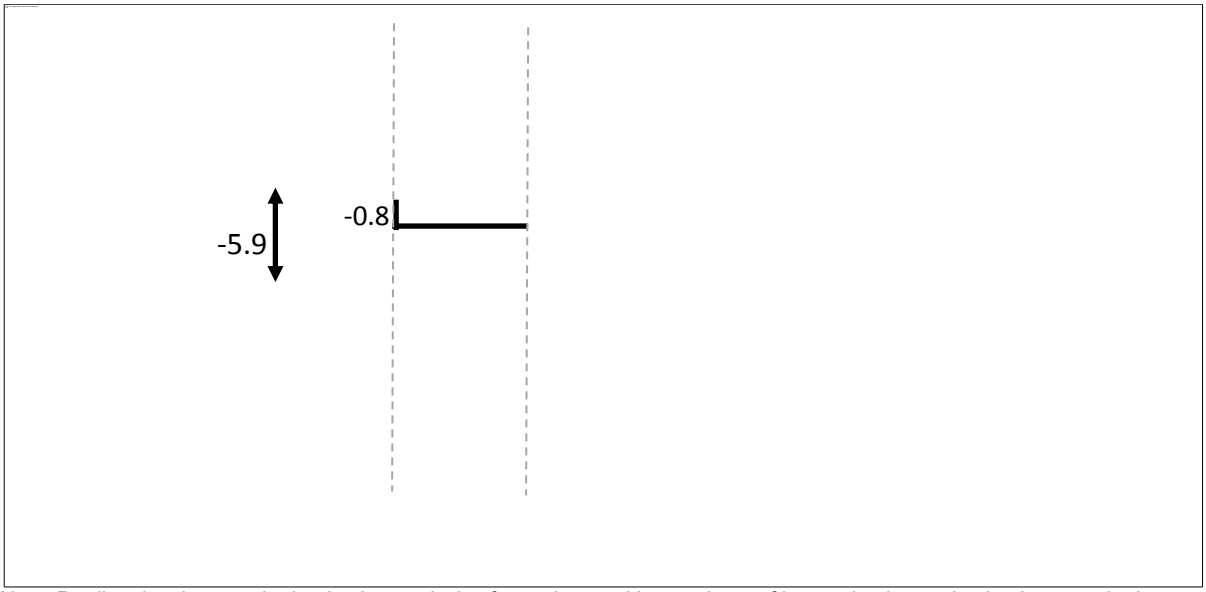
SGRQ – new analysis: isolating the benefit on HRQoL over and above exacerbation rate reduction

A new analysis was performed looking at the quality of life benefit patients experienced after adjusting for any change in exacerbation rate and the associated SGRQ benefit (analysis of covariance with covariates of baseline SGRQ, absolute reduction in exacerbations versus previous year, and treatment to predicted estimates change in SGRQ independent of exacerbation reduction). This was done in the MENSA ITT population to maximise the potential sample size.

In this analysis, mepolizumab (100mg SC & 75mg IV) showed a clear and clinically meaningful quality of life benefit in SGRQ of -5.9 (95% CI -8.7,-3.1), independent of the impact of a reduction in exacerbations when compared to placebo (

Figure 1). The impact on SGRQ of reducing the rate of exacerbations by 1 exacerbation per year was an improvement of 0.8 points (95% CI -1.3,-0.3) per exacerbation reduced. Therefore although part of the QoL benefit for patients on mepolizumab will be due to a reduction in exacerbations, there is HRQoL benefit from add-on mepolizumab therapy over and above this.

Figure 1 Change from baseline SGRQ by absolute reduction in exacerbations compared to previous year (100mg SC & 75mg IV combined, ITT MENSA)



Note: Predicted estimates obtained using analysis of covariance with covariates of base, absolute reduction in exacerbations versus previous year, and treatment (Change in exacerbation rates in previous year 0 = -0.5 to <0.5, 1 = 0.5 to <1.5, 2 = 1.5 to <2.5, ≥3 = ≥2.5).

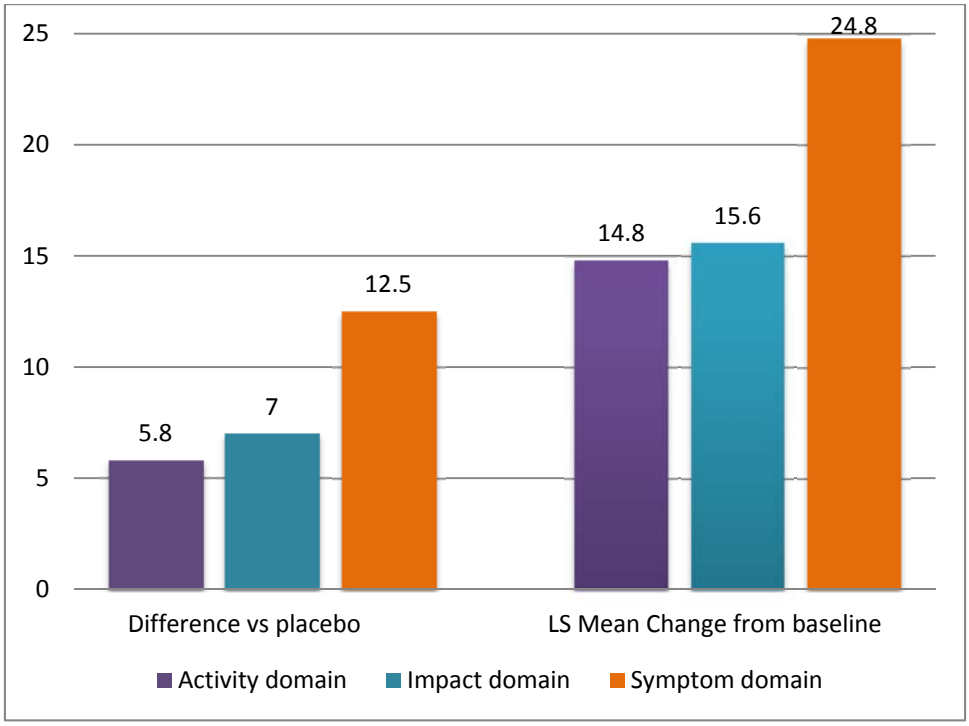
We recognise this is an exploratory analysis however the extent of the symptom benefit observed from add-on mepolizumab, beyond that resulting from a reduction in exacerbations, supports clinical feedback and clinical trial data - that the QoL benefits are not only due to a reduction in exacerbations.

SGRQ – new analysis: domain scores

An additional new analysis of MENSA was conducted to look at the SGRQ domains in the accepted population (analysis of covariance [ANCOVA] with covariates of treatment baseline, region and baseline percent predicted and FEV1). The frequency of respiratory symptoms domain was the key driver of the total SGRQ score (

Figure 2, Table 5). This provides further evidence supporting that add-on mepolizumab has a major effect on patients daily symptoms (-24.8 from baseline and -12.5 compared to placebo, 100mg SC).

Figure 2 Analysis of difference versus placebo in SGRQ score by domain versus placebo and from baseline (accepted sub-population, 100mg SC, MENSA)



Note: Analysis of MENSA performed using analysis of covariance (ANCOVA) with covariates of treatment baseline, region and baseline percent predicted FEV1

Table 5 Analysis of Change From Baseline in SGRQ Score by Domain (accepted sub-population, MENSA)

		Placebo	*100mg SC*	*75mg IV*
Activity domain	**n**	**64**	**91**	**74**
	LS Mean (SE)	50.9 (2.58)	45.2 (2.17)	45.3 (2.41)
	LS Mean Change (SE)	-9.1 (2.58)	-14.8 (2.17)	-14.7 (2.41)
	Diff vs placebo (95% CI)		**-5.8 (-12.4,0.9)**	**-5.6 (-12.6,1.4)**
Impact domain	**n**	**64**	**92**	**74**
	LS Mean (SE)	31.9 (2.07)	24.9 (1.74)	24.0 (1.94)
	LS Mean Change (SE)	-8.6 (2.07)	-15.6 (1.74)	-16.4 (1.94)
	Diff vs placebo (95% CI)		**-7.0 (-12.3,-1.7)**	**-7.8 (-13.5,-2.2)**
Symptom domain	**n**	**64**	**92**	**74**
	LS Mean (SE)	51.3 (2.89)	38.8 (2.41)	40.2 (2.70)
	LS Mean Change (SE)	-12.3 (2.89)	-24.8 (2.41)	-23.5 (2.70)
	Diff vs placebo (95% CI)		**-12.5 (-19.9,-5.1)**	**-11.2 (-19,-3.4)**

Note: Analysis of MENSA performed using analysis of covariance (ANCOVA) with covariates of treatment baseline, region and baseline percent predicted FEV1. Subjects with >=0.30 GI/L Blood Eosinophils at Baseline or Anytime in the Past 12 Months and either >=4 Exacerbations in Past Year or Maintenance OCS Use

1.2.2. Subject- and clinician-rated overall evaluation of response & other measures

A tertiary endpoint in both pivotal phase III trials (DREAM and MENSA) included a question while blinded to treatment to both the Investigator and subject, asking about their overall evaluation of treatment response. A 7-point scale was utilized ranging from significantly improved, moderately improved, mildly improved, no change, mild worsening, moderate worsening, significant worsening. In both studies, the odds ratio (OR) of reporting an improvement vs. standard of care plus placebo statistically significantly favoured mepolizumab across all doses. This simple question highlights that both physicians and patients perceive an overall significant benefit of treatment with mepolizumab.

There are also numerical improvements in reduced rescue medication use, daily asthma symptom scores and number of night time awakenings. Asthma-related quality of life is a global measure of the impact of asthma. Single domain measures, such as these are less sensitive and relevant to measuring symptom improvement in this severe population with long-term use compared to composite measures, (1) e.g. SGRQ and ACQ. (For full results, see Appendix A).

In summary, data have been presented, including new analyses highlighting mepolizumab's benefit on symptoms over and above the benefit received from reducing exacerbations. This provides additional evidence and aligns with the ERG's report and the clinical community's opinion, that add-on mepolizumab has a direct positive effect on HRQoL in addition to exacerbation reduction benefit.

We therefore ask the committee to reconsider its position (ACD section 4.23), and include the impact of symptom improvement, in addition to that of exacerbations.

1.3 *EQ-5D*

Assumption in ACD	ACD2 preferred assumption	Revised company base case	Justification
EQ-5D (ACD section 4.22) Preferred to SGRQ	✓	✓	Recognise the committee's preferences for direct EQ-5D. Baseline adjusted values presented

In the original submission, EQ-5D data captured in DREAM was included in the economic model only as a sensitivity analysis; given the ceiling effects seen with this instrument the base case used EQ-5D values mapped from SGRQ captured in MENSA. However GSK acknowledges that the committee would prefer directly derived EQ-5D values from a trial (ACD section 4.22), and as such, the revised base case uses EQ-5D values captured from the Phase IIb DREAM trial.

Closer scrutiny of the direct EQ-5D data from DREAM revealed a difference in baseline values between the mepolizumab and SoC arm in the accepted population. Baseline EQ-5D values for SoC were higher (0.794) than those in the mepolizumab group (0.716). Thus while the between group difference throughout the trial were relatively small (0.005) the

mepolizumab patients improved substantially (+0.081) from baseline while the SoC group decreased slightly (-0.002).

To account for this, baseline adjusted results were obtained using standard statistical methodology (least squares means) from a mixed model of repeated measures with covariates of treatment, age, visit, baseline and interaction between treatment and visit and visit and baseline. This model predicts placebo EQ-5D values of 0.765 for placebo and 0.804 in mepolizumab; giving a difference between placebo and mepolizumab of 0.039. This still provides a more conservative assumption than using the EQ-5D values mapped from the SGRQ data (0.07).

Table 6 Revised data inputs for EQ-5D to account for baseline imbalance, mean (SE), DREAM

Timepoint	SoC	Mepo 75mg IV
Observed		
Baseline	0.794 (0.024)	0.716 (0.034)
Post baseline	0.792 (0.026)	0.797 (0.023)
Diff between baseline and post baseline	-0.002	0.081
Diff between SOC and mepo		0.005
Baseline-Adjusted		
Baseline	0.747	0.747
Post baseline	0.765 (0.020)	0.804 (0.020)
Diff between baseline and post baseline	0.018	0.057
Diff between SOC and mepo		0.039

**It should be noted that this difference in baseline levels of EQ-5D between the two groups is not reflected in other differences in baseline characteristics on the groups which are otherwise well matched (Table 5, Appendix B).*

Limitations of the EQ-5D

Whilst we use the EQ-5D in our revised company base case, there is good reason to believe that doing so leads to an overly conservative estimate of the health related quality of life (HRQoL) benefit of mepolizumab.

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, using a mapping equation, (2) the issue of this ceiling effect from the EQ-5D is addressed to some degree. 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, one third of patients reported perfect health on the EQ-5D at baseline despite their disease severity. However, nobody in MENSA scored a zero in SGRQ, i.e.

nobody placed themselves in the best possible health state: as can be seen in Table 4, the minimum score was 5 in mepolizumab and 15 in the placebo arms. This was also the case in SIRIUS, where the minimum score was 8.

In the one third of patients from DREAM who reported perfect health using the EQ-5D, it is not possible to capture any improvement in HRQoL. However, patients reporting 'perfect health' in EQ-5D can have less than perfect health as measured and picked up by the SGRQ. Mapping SGRQ to EQ5D may therefore help discriminate between patients with no apparent improvements in EQ-5D and help quantify the quality of life benefit (or decrement) perceived by these subjects which would otherwise be unobservable due to limitation of the EQ-5D-3L instrument (ceiling effect and a limited number of levels).

For example,

- If a subject were to report perfect health across two time points in the EQ-5D, there would be no improvement in quality of life observed from EQ-5D.
- However, if this subject recorded a change in SGRQ at the same time points, the SGRQ (and mapping from it) can quantify this improvement (or decrement) which could not be observed through EQ-5D only: if the patient reported a change from 40.9 to 33.3 on the SGRQ, this would be interpreted as a 0.07 improvement in EQ-5D after mapping.
- Thus, where 30% of the population has no change in EQ-5D, using the EQ-5D leads to a dilution of the treatment benefit at a population level

Using SGRQ and the mapping of SGRQ to EQ-5D therefore helps quantify HRQoL in patients who apparently have no change in quality of life according to the EQ-5D, and thus a more representative HRQoL benefit at the population level. We recognise the committee's concerns with using SGRQ data mapped to EQ-5D, however we believe this does have some relevance to quantify the potential implication of the ceiling effect in EQ-5D and therefore it is presented as a sensitivity analysis. The 'most plausible ICER' is expected to lie between the baseline-adjusted direct EQ-5D and the mapped EQ-5D ICERs.

1.4 *Age adjusted utilities*

Assumption in ACD	ACD2 preferred assumption	Revised company base case	Justification
Age adjusted utility (ACD section 4.23) Utility adjusts with age	✓	**A**	Trial data shows that there is no evidence of utility being affected by age

In section 4.23 of the ACD, the committee considered that utilities should be age adjusted. It is understood that the ERG suggested that age adjusted utilities should be used in the analysis in order to ensure that nobody in the model states have a HRQoL greater than that observed in the general population (which in the model happens infrequently).

Whilst this adjustment has only a small effect on the ICER, it is a conservative adjustment applied by the committee. In order to assess its validity in the context of this model, the trial

data were analysed by age to see if there were differences observed across different age bands, within the SoC arm.

Table 7 Analysis of age on EQ-5D, observed and baseline adjusted values in DREAM ITT, SoC group, mean (SE)

	Observed		Baseline Adjusted	
Age category	**Pre week 16**	**Post week 16**	**Pre week 16**	**Post week 16**
25-35	0.835 (0.061)	0.725 (0.131)	0.764 (0.032)	0.767 (0.026)
35-45	0.716 (0.084)	0.756 (0.092)	0.763 (0.028)	0.767(0.021)
45-55	0.807 (0.038)	0.791 (0.043)	0.763 (0.026)	0.766 (0.020)
55-65	0.803 (0.037)	0.800 (0.044)	0.763 (0.028)	0.766 (0.022)
≥65	1 (n/a*)	0.922 (n/a*)	0.762 (0.033)	0.765 (0.026)
				*n=1 so no SE

As Table 7 shows, there was no difference observed between age and EQ-5D, across different age groups. As there is no evidence to support age adjusting utilities in this population, this assumption is not included in the company base case. Sensitivity analyses were however conducted to show the impact of including/excluding it from the base case, for completeness.

1.5 *Age adjusted mortality*

Assumption in ACD	ACD2 preferred assumption	Revised company base case	Justification
Age adjusted mortality There is an impact of age on asthma mortality	✓	✓	New data shows that there is an impact of asthma mortality on age

The ACD reports (section 4.24) on a preference by the committee for applying age related stratifications to mortality above the age of 45 years. A study to replicate the Watson analysis was conducted to provide additional data for age bands above the age of 45 years.

A retrospective cohort study using the same database as the original Watson study (CHKS) was conducted. All patients admitted (emergency admission only) with specific asthma related code J46 (‘‘acute severe asthma’’; status asthmatics) as primary reasons their first episode within a spell were included, within the time period April 1, 2000–March 31, 2015. The numbers of deaths post admission and the number of admissions were obtained, and a probability of death given an admission was calculated.

The age stratification on mortality above the age of 45 years is presented in Table 8. The data illustrates that there is a higher risk of mortality post asthma admission in those aged over 65 years in particular.

The new analysis shows that there is slightly lower probability of mortality across the age groups, than used by the ERG, which would translate into a slightly higher ICER (Section 2). These figures will be used in our revised base case.

Table 8 Results from new asthma related mortality data stratified by age

Age	Probability	Deaths post admission, n	Admissions, n	ERG estimated probabilities
0-11	0.0007	9	13,348	0.0015
12-16	0.0018	5	2,844	0.0014
17-44	0.0030	52	17,601	0.0020
45-54	0.0092	45	4,875	0.0076
55-64	0.0152	48	3,152	0.0214
≥65	0.0455	188	4,136	0.0454

1.6 *Continuation criteria*

Assumption in ACD	ACD2 preferred assumption	Revised company base case	Justification
Continuation Criteria: (ACD section 4.15) • **original** • **50% reduction** • **30% reduction**	**R**	✓	Reflects committee's preference for a continuation criteria linked to improvement

We note that

'*the committee concluded that continuation criteria linked to improvement would have been more appropriate*' (4.15).

This preference was supported by the severe asthma clinical community in their response to ACD1 as well as in our consultations with leading severe asthma specialists. The UK severe asthma clinical community have underlined their preference for a continuation criteria where mepolizumab is continued after 12 months if there has been a clinically meaningful reduction in exacerbation frequency or a reduction in maintenance OCS dose.

To align with the committee's and clinical opinion, we therefore propose a continuation criteria that is more explicitly defined and consistent with the mepolizumab marketing authorisation, the clinical trial data, and clinical practice.

1.6.1. Defining a continuation criteria based on improvement

Clinically meaningful reduction in exacerbation rate

Original criterion

In our original submission we defined the continuation criterion as '*annualised exacerbation rate improves or remains the same at 12 months*'. We are including this in our revised base case, to enable the committee to consider the impact of the other aspects of our response.

50%

Severe asthma specialists, in their response to the first ACD, recommended that a 50% reduction in exacerbation rate should be applied as continuation criteria. Also in the phase IIb/III RCTs a 50% reduction in exacerbation rate was observed with mepolizumab treatment. Similar mean reductions were achieved for the more severe exacerbations requiring emergency department (ED) visit or hospitalisation. In order to align with the specialist community's preference for a continuation criteria with a 50% exacerbation reduction threshold at 12 months, we will present the relevant clinical and cost-effectiveness results.

30%

As previously outlined in the company submission (section 4.7), there is evidence that a 30% reduction in exacerbations represents a clinically meaningful benefit in patients with severe asthma who are uncontrolled on maximal SoC therapy (see Appendix C). This slightly lower threshold may allow for more clinical judgement to be applied in the context of other clinical factors such as improvement in their asthma control and quality of life, whilst allowing more patients with frequent exacerbations to continue on treatment. We will therefore also present clinical and cost-effectiveness results for a continuation criteria requiring a 30% reduction in exacerbation rate at 12 months.

Reduction in mOCS dose

Whilst guidelines recommend reducing a patient's OCS dose to the lowest possible level, after discussions with severe asthma specialists, a clinically meaningful reduction in maintenance OCS dose is more difficult to define. This is dependent on local clinical practice as well as individual patient factors, such as baseline maintenance dose, co-morbidities and adrenal suppression. Thus, the rate and level of reduction in OCS dose defined as clinically meaningful will be different from patient to patient.

Moreover, as discussed in the company submission and acknowledged by the committee, the current evidence base does not allow the economic model to include the clinical and cost-effectiveness to the NHS that would be seen from reducing patients' OCS exposure.

We would therefore suggest a pragmatic OCS continuation criterion refined slightly from our original submission that will allow for individualised patient centred management, defined as: *a reduction in maintenance oral corticosteroid dose while maintaining asthma control*. In SIRIUS, in our accepted population, 66% achieved a reduction in mOCS dose while maintaining asthma control (100mg SC).

Mepolizumab's licence states: *The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations* (as per SmPC section 4.2).

In consideration of the license and the factors outlined above, best clinical practice and the severe asthma specialist community in the UK, we recommend the committee to consider a

continuation criteria that will allow appropriate identification of patients with a clinically meaningful benefit from add-on mepolizumab treatment, and thus should be continued on this therapy. We propose the following wording for a continuation criteria:

- *Mepolizumab therapy should be continued if at 12 months from initiation of treatment:*
  - *A 50% (or 30%)* ***reduction in the number of exacerbations*** *is observed compared to the prior 12 months*

    OR
  - *A* ***reduction in maintenance oral corticosteroid dose*** *is observed while maintaining asthma control*

1.6.2. Supporting Data for the Revised Continuation Criteria

Analysis assessing the appropriateness of applying a continuation criterion based on an improvement of 50% (or 30%) in annual exacerbation rate, using 84 weeks of clinical trial data

We are able to demonstrate the appropriateness of applying a continuation criterion based on reducing exacerbations by 50% (or 30%) using mepolizumab patient level trial data, which covered almost a 2 year period. Patients were treated on mepolizumab for 8 months in MENSA and continued for a further 12 months in the open label extention (OLE) study, COSMOS.

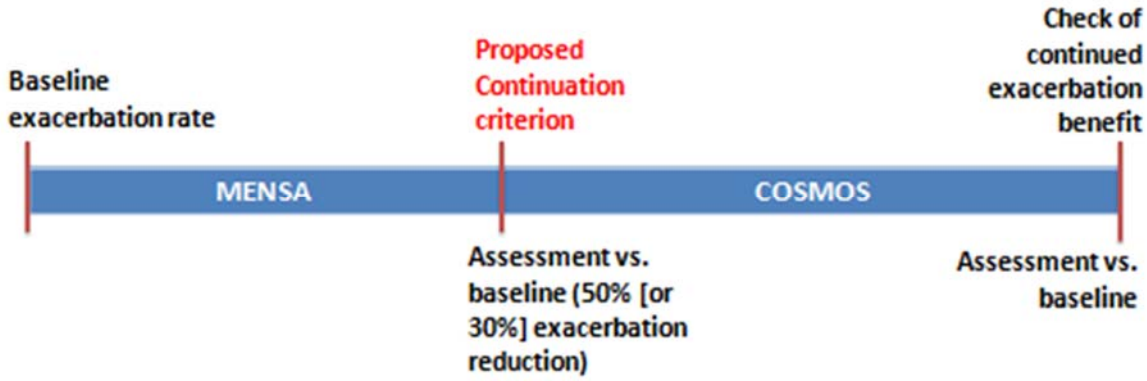
- The continuation criterion was applied to the accepted sub-population on add-on mepolizumab treatment at the end of MENSA. Patients were categorised as 'met' if they had a 50% (or 30%) reduction in exacerbation rate at the end of MENSA compared to baseline, or 'not met' if they did not achieve that 50% (or 30%) reduction (i.e. 'met' = patients who would continue on treatment in the real world after 12 months and 'not met' = patients who would stop in the real world).
- For the purpose of this analysis only, patients who both 'met' and 'not met' the continuation criterion at the end of MENSA were then assessed again at the end of COSMOS, and categorised as 'met' if they had a 50% (or 30%) reduction in exacerbation rate at the end of COSMOS compared to baseline before MENSA or 'not met' if the did not achieve that 50% (or 30%) reduction.

This methodology (further explained in

Figure 3) allows for an objective assessment of whether a 50% (or 30%) reduction in exacerbation rate acheived at 12 months is still maintained (or improved) in the following year. It also shows whether those patients that don't receive sufficient benefit in year 1 (end of MENSA) (and would therefore discontinute treatment in the real world), would go on to

have received benefit in year 2 (end of COSMOS). The results of this analysis are shown in Table 9.

Figure 3 Methodology of percentage reduction in exacerbation continuation criteria analysis using MENSA and COSMOS data



Although the duration of MENSA (8 months) was shorter than the proposed continuation criteria to be applied at 12 months, using the above methodology still informs on the validity of applying this continuation criteria, given it applies an annualised exacerbation rate. Additional points supporting the use of MENSA data to inform on a 12 month based continuation criteria are:

- In DREAM, a 12 month exacerbation study, a consistent and similar reduction in exacerbations was observed: 48% with 75 mg IV at 12 months in DREAM compared to 47% with 75 mg IV (53% with 100 mg SC) at 8 months in MENSA.
- Treatment response with mepolizumab is only marginally affected by seasonal changes in exacerbation frequency [Ortega, 2014], thus the 8 months MENSA trial was deemed sufficient to inform of mepolizumab's effect on annual exacerbation rates.
- The regulators accepted the use of MENSA as a key licensing study and proposed a 12 month treatment review based on this evidence.

Table 9 Summary of subjects in the accepted subgroup treated with mepolizumab meeting and not meeting a 50% (or 30%) reduction in exacerbations in MENSA and COSMOS, compared to the baseline exacerbation rate the year prior to MENSA.

	MENSA	COSMOS

Continuation criteria	**Met / not met percentage reduction in exacerbations at end of MENSA, n (% of total population, n=159)** ***(Continuation criteria)***		**Met / not met percentage reduction in exacerbations at end of COSMOS, n (% of total population, n=159)** ***(post continuation criteria)***	
			Met	**Not met**
≥50% reduction in exacerbation rate vs. baseline	Total n	159	121 (76)	38 (24)
	Met	122 (77)	103 (65)	19 (12)
	Not met	37 (23)	18 (11)	19 (12)
≥30% reduction in exacerbation rate vs. baseline	Total n	159	136 (86)	23 (14)
	Met	134(84)	124 (78)	10 (6)
	Not met	25 (16)	12 (8)	13 (8)

Percentages in rows and columns are in relation to the total number of subjects (N=159).

Results for those meeting continuation criteria

Applying the continuation criteria to the accepted sub-population showed that after MENSA, 77% (122/159) achieved a 50% reduction and 84% [134/159] achieved a 30% reduction in exacerbation rate (Table 9).

Importantly, 65% (103/159) of patients in the accepted sub-population met the 50% continutation criteria in MENSA and continued to benefit in COSMOS (78% [124/159] continued to benefit for 30%) (Table 9).

Results for those not meeting continuation criteria

At the end of MENSA, 23% (37/159) did not achieve a 50% reduction in exacerbation rate and 16% [25/159] did not achieve 30% reduction.

12% (19/159) of patients in the accepted sub-population did not achieve a 50% reduction in exacerbations in both in MENSA and COSMOS (8% [13/159] did not achieve a 30% in MENSA and COSMOS) (Table 9).

Given there is some inevitable variation in asthma control, the results above give reassurance that a continuation criteria based on percentage reduction in exacerbations is a reasonable approach. Applying the 30% threshold has the benefit that the chance that you discontinue someone who has not yet received benefit, but may do so in the future, is lower than with the 50% rule. However with the 50% threshold the number of patients that discontinue but may have had benefit in the future is still low, and this level is more in line with the asthma specialists' views on a clinically meaningful reduction. Both criteria align with mepolizumab's licence, and are consistent with the committee's preference for a continuation criteria based on improvement.

1.6.3. Summary of proposed continuation criteria based on Guide to the Methods of Technology Appraisal 2013

Considerations for the continuation criteria (5.10.12 Guide to the methods of technology appraisal 2013)	**GSK Considerations**
...the robustness and plausibility of the end point	Exacerbations are cited as an appropriate basis

on which the criteria is based	for a continuation criterion in the SmPC. Given the specialist nature of severe asthma management there is a consistent understanding of what constitutes an asthma exacerbation. The criteria also include patients reducing oral steroid dose as this is a recognised alternative benefit of treatment.
...whether the 'response' criteria defined in the rule can be reasonably achieved	It was achieved in mepolizumab clinical trial data, for the accepted population in MENSA, showing that 77% of patients experienced a ≥50% reduction in exacerbations (84% of patients experienced a ≥30% reduction).
...the appropriateness and robustness of the time at which response is measured	The time-point is as recommended in the SmPC. The criterion is implemented using annualised exacerbation rates based on the MENSA trial. The EMA approved the license & recommended a 12 month review based on these data.
...whether the rule can be incorporated into routine clinical practice	Patients will be seen on a 4 weekly basis to receive treatment, and monitoring of exacerbations and steroid use would form part of a standard review of the patient's response to therapy. Therefore it can be easily incorporated into routine clinical practice.
...whether the rule is likely to predict those patients for whom the technology is particularly cost effective	The criterion improves cost-effectiveness and reflects the committee's preference for a continuation criterion based on improvement.
...considerations of fairness with regard to withdrawal of treatment from people whose condition does not respond to treatment.	The SmPC states, "The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations". The severe asthma community have commented that a 50% reduction in exacerbations is a clinically appropriate level to review treatment. Whilst our analysis demonstrates that a few patients if allowed to continue may have received clinical benefit in the following year, they only represent a small proportion of the patient population. Given the nature of this variable heterogeneous disease any review is likely to have this implication and needs to be viewed in the context of balancing risk/benefit to patients when using a biologic.

1.6.4. Implementing the revised continuation criterion in the economic model

The previous continuation criterion, of no worsening in exacerbation rate, was therefore revised to take into account the committee's preference that '*linked to improvement would have been more appropriate*' (ACD section 4.15). The same approach preferred by the committee for estimating exacerbation rates post continuation assessment were used, identifying patients meeting the criteria in MENSA and using COSMOS data for the exacerbation rates and the adjustments for SoC (ACD Section 4.19). In the context of the model inputs, new data were obtained for exacerbation rates, utilities and for the number of people meeting the continuation criteria, using a threshold of 50% (and a threshold of 30%). The model inputs are summarised in Table 10. The model inputs for the two continuation

criteria were applied to the revised company base case and the results are presented in section 2.

Table 10 Model inputs, continuation criteria

Variable		Mean	SE	Source
Exacerbation parameters				
Patients meeting mepolizumab continuation criteria				
No reduction - exacerbations	Rate	1.020	0.114	COSMOS from MENSA
50% reduction	Rate	0.890	0.132	COSMOS from MENSA
30% reduction	Rate	1.020	0.124	COSMOS from MENSA
Not meeting continuation criteria				
No reduction - exacerbations	Rate	5.260	0.248	COSMOS from MENSA
50% reduction	Rate	3.270	0.182	COSMOS from MENSA
30% reduction	Rate	3.720	0.225	COSMOS from MENSA
% patients meeting mepo continuation criteria				
No reduction - exacerbations	p%	0.892	0.023	MENSA
50% reduction	p%	0.767	0.034	MENSA
30% reduction	p%	0.843	0.029	MENSA
Utility parameters				
Meeting Continuation criteria				
No reduction - exacerbations	Utility	0.806	0.023	DREAM
50% reduction	Utility	0.823	0.023	DREAM
30% reduction	Utility	0.824	0.023	DREAM

Rationale for not applying the mOCS part of the continuation criteria to the model

Because in MENSA, dosing of mOCS was optimised at baseline and patients were not allowed to reduce their dose during the trial, it was not possible to robustly apply the second part of the rule with the data that are available. We therefore applied the exacerbation-based criterion described above to the total accepted population.

1.6.5. Approach to Attrition

In addition to the continuation criteria at 12 months on treatment, a 10% annual attrition rate is applied annually to the model from year 2 onwards. In section 4.15 the committee raised concerns that this figure seemed to be arbitrary. This figure was actually taken from our open label extension study COSMOS, which is likely to be reflective of long term clinical practice, where 10% of patients withdrew from treatment with mepolizumab (66/651). The ACD section 4.15 suggests assuming higher attrition rates would increase the ICER. Sensitivity analyses were previously conducted which adjusted the attrition rate and has shown that the ICERs remained relatively stable.

In summary, based on the information outlined above, we ask the committee to consider a continuation criteria that will allow appropriate identification of patients that receive clinically meaningful benefit from add-on mepolizumab treatment, to be continued on this therapy. Base case cost-effectivness results are provided in Section 2, showing the original continuation criterion, and exploring the impact of the 2 thresholds proposed.

1.7 *Other aspects in the ACD*

1.7.1. Age of eosinophilic asthma patients in the UK

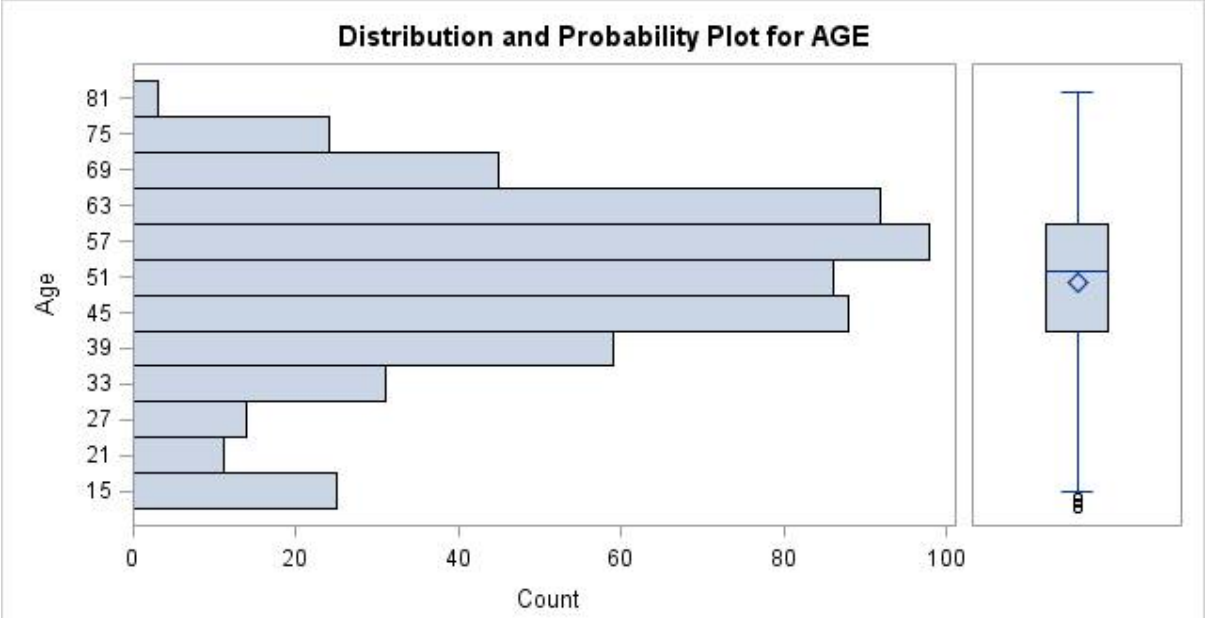
Assumption in ACD	ACD2 preferred assumptions	Revised company base case	Justification
Age (ACD section 4.25) Model start age of 50.1 years	**R**	✓	The committee noted that the impact on the ICER was marginal, so kept at 50.1

In the revised company base case, for the economic model, GSK have aligned with the ACD section 4.25 on age, and kept the starting age at 50.1 years.

The ACD does however suggest that age in the model (of 50.1 years) was likely to be older than that seen in clinical practice. However the proposed population for mepolizumab is a recognised phenotype, specifically late-onset eosinophilic disease. This is generally non-atopic, refractory to inhaled steroids and more likely to require long term systemic corticosteroids. A BTS Registry study showed that late onset eosinophilic phenotype affects an older more established asthma population. People with late onset eosinophilic disease generally have had asthma for many years, but it is only when they are older that their asthma changes to be severe. When looking at a cohort of 245 people, late-onset, eosinophilic asthma was identified as a distinct category (n=32), with a mean (SD) age at baseline of 49 (14.6) years, and age at onset of symptoms was 34.5 (16.5) years (3). Note this compares with early-onset, atopic asthma (typically treated with omalizumab), with a mean age of 40.2 (13.7) years, with strikingly, an age at onset of symptoms of 10.2 (9.97) years (3). A more recent Thorax (2016) publication looking at two UK severe asthma populations, confirmed a mean age of 50 (14.5) years in 770 BTS registry patients (data collected from UK dedicated Specialist Difficult Asthma Services) and a mean patients age of 59 (17) in the Optimum Patient Care Research Database (n=808), a UK respiratory database containing anonymised primary care data (4).

Given the cohort defined in the proposed population may be primarily late-onset, descriptive data from MENSA were generated to describe the distribution of age in the trial and so in this population (Figure 4). This cohort was seen to have a skewed distribution, such that the mean age of 50.1 years (as shown by the diamond in the plot), is younger than the median age of 52.0 years, which in turn is younger still than the modal age of 60.0 years.

Figure 4 Age distribution in MENSA



The new analyses on age-adjusted mortality, as described above, together with the demographics of people with late-onset eosinophilic asthma, indicate that this population are likely to be at an elevated risk of death from asthma mortality. As such, it is useful to also consider which average statistic of age we use to model this specific phenotype of the disease. To account for this skewed distribution, in a sensitivity analysis, we assessed the impact of using the median age of 52.0 years rather than the mean age of 50.1 years. In section 2 this shows that an increase in age to 52 years is associated with a small reduction in the ICER.

Therefore we believe a starting age of 50.1 years in the model is reasonable, and is appropriate for use in the base case

1.7.2. Consideration of waning of treatment effect

In Section 4.26 the committee assumed a waning effect was likely to increase the ICER. However in our revised base case no change to the original model assumptions have been made. This assumption is supported by data from the COSMOS study (5), which showed that patients continue to benefit in terms of exacerbation rate, mOCS reduction and ACQ without a waning effect when continued on add-on mepolizumab treatment. Furthermore, as previously explained, 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 assumption of continued effectiveness was discussed at the committee meetings and was supported by the clinical experts present during the initial meeting. In addition, with more than 10 years of clinical experience in the UK using omalizumab, the only other biologic in severe asthma, there has been no evidence of potential waning with therapy. Therefore we believe in the absence of any evidence to the contrary, this should not be considered as an ongoing uncertainty in the analyses.

1.7.3. Accounting for reduction in maintenance OCS use

Assumption in ACD	ACD2 preferred assumptions	Revised company base case	Justification
mOCS benefit (ACD section 4.28)	**R**	✓	Tries to quantify the benefits of avoiding mOCS use. Included as variation to base case.

The committee acknowledged the significant adverse effects of oral corticosteroid use, and that this had not been fully captured in the QALY measure. We agree that the long-term health benefits of reducing OCS exposure are difficult to capture fully in the economic evaluation. This has been recognised as a challenge in NICE appraisals across a range of disease areas. Even small reductions in mOCS dose can potentially have significant benefit to patients. Patients on <5mg/day have much larger odds of developing associated complications (OR 2.50), with an almost doubling incidence rate ratios for inpatient visits (RR 1.86) (6).

In considering how to quantify this benefit, we looked to the approach taken in TA278 (omalizumab), which modelled the costs and consequences of OCS in severe asthma, and which we can consider to have some relevance with respect to the potential scale of the impact. This analysis reduced the reported base case ICER by between £4,000 and £6,000 in two of the resulting published articles from the assessment (7;8), and by between £10,000 and £17,000 per QALY gained in the assessment report. (9) One of these values was adopted (subtracted from the pre mOCS ICER), to give the most plausible ICER for the omalizumab appraisal. From the detail contained within the FAD, it is not clear which, and so we present a reduction of £4,000-£9,000 to the ICER as an additional scenario to our base case analyses. Whilst we acknowledge this to be a crude estimate, this helps to quantify the potential impact of the mOCS sparing effect. Accounting for this treatment benefit would significantly improve the base case ICER.

1.8 *Comparison with omalizumab*

We acknowledge the change in the ACD which reflects the evidence that mepolizumab is effective in patients that have previously received omalizumab. However we remain concerned over the rejections of the comparison with omalizumab.

In Section 4.10 the committee have decided not to consider the comparison between mepolizumab and omalizumab further due to uncertainty in the evidence (primarily resulting from the lack of availability to us of patient level data for omalizumab) and also because feedback from clinicians did not consider the comparison appropriate as few patients would be likely to have either drug. We agree that the overlap population that would be eligible for either mepolizumab and omalizumab is relatively small and that given the distinct phenotypes involved, patients would tend to be offered the treatment most appropriate to their presenting symptoms if both were available on the NHS. However if the current draft negative recommendation for mepolizumab by NICE is confirmed, this will not be the case as those patients more appropriate for mepolizumab would not be able to be prescribed this

treatment. Therefore clinicians would have no option but to either prescribe omalizumab, or continue with SoC, which is likely to involve an increased use of oral corticosteroids and their associated significant side-effects.

As a result of this initial decision by the committee no further consideration has been made of the relative cost effectiveness evidence that has been provided (Section 4.13). We believe that in the context of draft negative guidance for mepolizumab it is important to also review this evidence including the impact of the updated PAS and the approach to uncertainty in the clinical evidence. In the analysis provided in our original submission utilising the original PAS price mepolizumab was dominant in most scenarios considered. In this response GSK has further improved the PAS price that is being offered and as a result mepolizumab is likely to be a cheaper option in all scenarios – even utilising the most conservative assumption on dose of omalizumab used in clinical practice (accuracy dependent on the confidential PAS price for omalizumab). We accept that there is some inevitable uncertainty in the estimates of relative effectiveness; however given the context that clinicians are likely to prescribe dependent on the presenting phenotype, we believe that the committee should consider providing guidance that will enable patients that meet the NICE criteria for omalizumab as well as mepolizumab to be able to be prescribed the most clinically appropriate option for them (and with mepolizumab at a cost saving to the NHS).

An underlying driver of the positive guidance for omalizumab and the current draft negative recommendation for mepolizumab is the differences in approach to the assumptions underpinning the cost effectiveness analysis accepted as most plausible by the respective committees. Whilst we agree that these appraisals concern different types of asthma, and the evidence base is evolving, the evidence underpinning the assumptions is primarily driven from common sources and there is no reason to believe that these are any more or less relevant for eosinophilic than atopic asthma. In the NICE *Guide to Methods of Technology Appraisals 2013*, it states that as far as possible judgements should be consistently applied between appraisals. If the preferred assumptions taken from the omalizumab MTA were incorporated in the analysis for mepolizumab, it would result in a highly cost effective medicine that therefore would likely be subject to positive NICE guidance.

In conclusion, we would therefore ask the committee to reconsider the comparative evidence in this context. To be clear, in proposing this we are not suggesting that mepolizumab should be made available in preference to omalizumab – only that in the overlap population clinicians should be able to prescribe the medicine that is most appropriate for people based on their phenotype as described in Section 4.10 of the ACD, given there would be no opportunity cost to the NHS of doing so.

2 Modeling the impact of the different model assumptions on cost effectiveness, and the revised company base case

As can be seen throughout this response, GSK has considered the committee's conclusions and concerns in ACD2, and has taken steps to generate new data, conduct further analyses, revise model inputs and offer a revised PAS to address these. The new elements, together with most of the adjustments to assumptions made by the committee, give a revised company base-case which is summarised in Table 11.

Table 11, Assumptions used in cost effectiveness model, ACD2 preferred and revised company base case (including revised PAS)

Key: ✓ = preferred and incorporated by committee / included in GSK base case
R = raised but not included in committee base case
A = not incorporated in GSK base case & alternative proposed

Assumption in ACD	ACD2 preferred assumption	Revised company base case	One way impact on the ICER from ACD2 preferred to revised company base case
Age Model start age is 50.1	**R**	✓	N/A
Treatment duration Lifetime	✓	✓	N/A
Exacerbations rates Source of exacerbation rates to be used post application of continuation criteria as per ERG proposals and committee's preference.	✓	✓	N/A
Duration of exacerbation Taken from MENSA relating to resource use	✓	**A** ***Midpoint Lloyd-MENSA***	-£2,012
Effect on symptoms No effect obtained on top of exacerbations	✓	**A** ***Utilising Direct EQ-5D***	-£7,644
EQ-5D Preferred to SGRQ	✓	✓ ***Utilising Baseline Adjusted EQ-5D***	-£11,314*
Age adjusted utility Utility adjusts with age	✓	**A** ***No Utility Age Adjustment***	-£1,350
Age adjusted mortality There is an impact of age on asthma mortality	✓	✓ ***New Mortality Evidence***	+£1,164

* change in ICER reflects move from 'Utilising Direct EQ-5D' to 'Baseline Adjusted EQ-5D'

These revised assumptions were applied to an amended model (which combined the ERG's previous adjustments with those adjustments set out in the revised base case). On top of these analyses, the committee's preference for a continuation rule linked to improvement was applied. In addition, explicit quantification of the potential mOCS benefit of between £4,000-£9,000 reduction on the ICER was presented (Table 12).

The analyses show that applying the revised company base case assumptions to the model for mepolizumab, together with the revised PAS, and the original continuation criteria gives a revised company base case ICER of **£31,724 per QALY gained** (Table 12).

When introducing a 50% continuation criteria, a base case ICER of **£27,418 per QALY gained** (Table 12) is obtained. Explicitly adding in benefits of mOCS as per TA278 reduction would bring the ICER down to between **£18,418 and £23,418 per QALY gained**. Applying a 30% continuation criterion leads to a slightly higher ICER of **£28,398 per QALY gained**, and between **£19,398 and £24,398** when adding in an explicit mOCS benefit.

Table 12. Results of cost effectiveness analyses for revised company base case, with different continuation criteria (including revised PAS)

Results	Δ Costs (£)	Δ QALYs	ICER (£)
Original Continuation Criterion	[redacted]	[redacted]	31,724
Revised Continuation Criteria, 50% Reduction	[redacted]	[redacted]	27,418
Revised Continuation Criteria, 30% Reduction	[redacted]	[redacted]	28,398
Results	**Δ to ICER**		**ICER (£)**
Revised Continuation Criteria, 50% Reduction, including mOCS benefit	-£4,000-£9,000		18,418-23,418
Revised Continuation Criteria, 30% Reduction, including mOCS benefit	-£4,000-£9,000		19,398 - 24,398

2.1 *Scenario analyses*

Four scenario analyses are presented to explore the uncertainties around the ERG and the company base case, assuming the original continuation criteria, and a 50% and 30% continuation criteria. The rationale and model inputs for each of these scenarios, have been explained and detailed in the relevant section of the response:

1. Using duration of exacerbations from MENSA rather than the midpoint of Lloyd and MENSA (see section 1.1)

2. Turning on the utility age adjustment, rather than being off (section 1.4)

3. Applying the EQ-5D mapped from SGRQ values, to indicate the potential scale of the ceiling effect (section 1.3)

4. Using the median age of the trial population (52 years), rather than the mean age (50.1 years) (section 1.7)

Table 13 Results of scenario analyses, revised base case, original continuation criterion (including new PAS)

Scenario				Proposed population		
1	2	3	4	Δ Costs (£)	Δ QALYs	ICER (£)
				[redacted]	[redacted]	**31,724**
			✓	[redacted]	[redacted]	29,837
		✓		[redacted]	[redacted]	24,205
	✓			[redacted]	[redacted]	32,301
✓				[redacted]	[redacted]	32,475
		✓	✓	[redacted]	[redacted]	23,212
	✓		✓	[redacted]	[redacted]	30,494
✓			✓	[redacted]	[redacted]	30,485
	✓	✓		[redacted]	[redacted]	24,353
✓		✓		[redacted]	[redacted]	24,640
✓	✓			[redacted]	[redacted]	33,080
	✓	✓	✓	[redacted]	[redacted]	23,392
✓		✓	✓	[redacted]	[redacted]	23,602
✓	✓		✓	[redacted]	[redacted]	31,171
✓	✓	✓		[redacted]	[redacted]	24,793
✓	✓	✓	✓	[redacted]	[redacted]	23,789

Table 14 Results of scenario analyses, revised base case, 50% continuation criteria (including new PAS)

Scenario				Proposed population		
1	2	3	4	Δ Costs (£)	Δ QALYs	ICER (£)
				[redacted]	[redacted]	27,418
			✓	[redacted]	[redacted]	25,886
		✓		[redacted]	[redacted]	22,178
	✓			[redacted]	[redacted]	28,134
✓				[redacted]	[redacted]	28,038
		✓	✓	[redacted]	[redacted]	21,275
	✓		✓	[redacted]	[redacted]	26,729
✓			✓	[redacted]	[redacted]	26,422
	✓	✓		[redacted]	[redacted]	22,357
✓		✓		[redacted]	[redacted]	22,582
✓	✓			[redacted]	[redacted]	28,788
	✓	✓	✓	[redacted]	[redacted]	21,494
✓		✓	✓	[redacted]	[redacted]	21,636
✓	✓		✓	[redacted]	[redacted]	27,302
✓	✓	✓		[redacted]	[redacted]	22,768
✓	✓	✓	✓	[redacted]	[redacted]	21,863

Table 15 Results of scenario analyses, revised base case, 30% continuation criteria (including new PAS)

Scenario				Proposed population		
1	**2**	**3**	**4**	Δ Costs (£)	Δ QALYs	ICER (£)
				[redacted]	[redacted]	28,398
			✓	[redacted]	[redacted]	26,862
		✓		[redacted]	[redacted]	24,206
	✓			[redacted]	[redacted]	29,175
✓				[redacted]	[redacted]	29,016
		✓	✓	[redacted]	[redacted]	23,193
	✓		✓	[redacted]	[redacted]	27,783
✓			✓	[redacted]	[redacted]	27,400
	✓	✓		[redacted]	[redacted]	24,356
✓		✓		[redacted]	[redacted]	24,654
	✓	✓	✓	[redacted]	[redacted]	23,376
✓		✓	✓	[redacted]	[redacted]	23,593
✓	✓			[redacted]	[redacted]	29,828
✓	✓		✓	[redacted]	[redacted]	28,358
✓	✓	✓		[redacted]	[redacted]	24,809
✓	✓	✓	✓	[redacted]	[redacted]	23,782

The analyses show that adjusting for these uncertainties results in ICERs between **£21,275 and £28,134** (50% reduction in exacerbations) and **£23,193 and £29,828** (30% reduction in exacerbations), depending on the assumptions applied. Utilising duration of exacerbations from MENSA (scenario 1) and adjusting utilities for age (2) slightly increase the ICER, whereas applying the EQ-5D mapped from SGRQ (3) and the median age of the trial population (4) can be seen to improve the ICER. When applying the new continuation criteria, in all scenarios, the ICERs are still within the range which NICE may consider a cost effective use of NHS resources.

In addition the committee has recognised that for this innovative medicine, there are elements of value that have not been well captured in the ICER. In particular, the significant benefit to patients of reducing oral steroid burden has not been included. We acknowledge that it is difficult to capture this in numerical terms. However, explicitly adding in benefits of mOCS as per TA278 reduction would bring the ICER down to between **£18,418 and £23,418 per QALY gained** (50% continuation criteria), and between **£19,398 and £24,398 per QALY gained** (30% continuation criteria). We acknowledge this is a relatively crude analysis, however it gives the committee an approximation of the scale of impact.

In addition, the potential benefits to carers have not been able to be quantified and could provide further improvement to cost effectiveness.

We therefore believe that mepolizumab in the accepted population, with a revised continuation criteria, provides a cost-effective use of NHS resources, and we ask the committee to reconsider its draft guidance.

3 Summary of factual inaccuracies

Description of inaccuracy	Description of proposed amendment	Justification for amendment
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%.
Section 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 to with a ”–“ sign
Section 3.45 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.”	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. We recommend to remove this statement.	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.
Section 3.48: Analysis 3 states, “patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year, and a blood eosinophil count of 300 cells/microlitre or more per year”.	Analysis 3 should state, “patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year, and a blood eosinophil count of 300 cells/microlitre or more in the previous year.	This re-wording just provides additional clarification on the proposed population.
Section 4.7: It states, “Having considered all the comments, the committee concluded that the population in analysis 3, that is, people with a blood eosinophil count of 300 cells/microlitre or more per year and at least one of the following...”	This sentence should be re-phrased to state, “Having considered all the comments, the committee concluded that the population in analysis 3, that is, people with a blood eosinophil count of 300 cells/microlitre or more in the previous year and at least one of the following...”	This re-wording just provides additional clarification on the proposed population.
Summary of appraisal, 4:10: “In addition, its guidance would not apply to asthma that has previously been treated with omalizumab because evidence for this position in the treatment pathway was not presented”. This is contradictory to what is stated in the Section 4.11.	In Section 4:11, it states “The company also presented further data from the MENSA trial stratified by prior omalizumab use, which showed that there is no evidence of differential effectiveness in people previously treated with omalizumab. The committee concluded that mepolizumab is effective in people previously treated with omalizumab”.	Our assumption is that the summary statement is incorrect and should be re-worded to that stated in 4.11.
Section 4.15: It states, “Also, the committee considered that a 10% attrition rate seemed to be arbitrary and did not constitute a formal continuation rule”	This sentence should be removed.	There are two reasons for this as the continuation rule and the attrition rate are two separate and distinct parts of the model: i) In year 1, a continuation rule, of no worsening in exacerbation rates was applied, to the subpopulation in MENSA, which found that 89.2%, met the rule, and 10.9% did not meet the rule (applying the initially proposed continuation rule). This is a specific review and would only take place at 12 months. ii) The 10% annual attrition rate is applied to the model from year 2 onwards. This figure is estimated based on the clinical trial programme for mepolizumab, specifically in the one year OLE study, COSMOS, where 10% of patients withdrew from treatment with mepolizumab (66/651). This assumption of attrition reflects that, consistent with good clinical practice, the ongoing need for treatment with mepolizumab will continue to be reviewed on the basis of

		risk benefit to the patients, as well as patient choice/non adherence. It is therefore not clear why the 10% attrition rate is regarded as arbitrary, and we suggest this statement be removed. . Thus it has never been suggested that the attrition rate would constitute a formal continuation rule, and so this sentence should be removed as it is factually inaccurate.

Below are some factual inaccuracies within Table 1 of Section 3.10. Corrected figures highlighted.

Table 1 from ACD2 Section 3.10 Clinically significant exacerbation rate ratios for mepolizumab compared to placebo

	Modified ITT population (95% CI)	**Proposed population (95% CI)**	**Restricted population (95% CI)**
MENSA (75mg IV)	0.53 (0.40 to 0.72)	0.40 (0.24 to 0.67)	0.39 (0.22 to 0.68)
MENSA (100mg SC)	0.47 (0.35 to 0.64)	0.50 (0.32 to 0.78)	0.39 (0.23 to 0.67)
MENSA pooled (75mg IV and 100mg SC)	0.50 (0.39 to 0.65)	Not reported	Not reported
DREAM (75mg IV)	0.52 (0.39 to 0.69)	0.36 (0.24 to 0.55)	0.31 (0.18 to 0.53)
SIRIUS (100mg SC)	0.68 (0.47 to 0.99)	0.77 (0.51 to 1.17)	0.81 (0.40 to 1.64)
DREAM + MENSA (75mg IV or 100mg SC)	0.51 (0.42 to 0.62)	0.41 (0.31 to 0.55)	0.35 (0.25 to 0.50)
DREAM + MENSA + SIRIUS (75mg IV or 100mg SC)	Not possible	0.50 (0.40 to 0.64)	0.42 (0.30 to 0.57)
Abbreviations: CI, confidence interval; ITT, intention to treat; IV, intravenous; SC, subcutaneous			

Factual inaccuracies in our response to ACD1 were found in Table 10 and 12 of Section 2.4. Please find the corrected tables below (Corrected figures highlighted):

ACD1 response: 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)	-17.0 (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	42	52
	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)	2.09 (0.152)	1.46 (0.140)
	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)	0.08 (0.152)	-0.54 (0.140)
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		-0.62
	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		-1.03, -0.21
	p value		0.183	0.02	0.085		0.543	0.076	0.097		<0.001	<0.001		<0.001	<0.001		0.004		0.003

ACD1 response: 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)	16 (23)	4 (8)	14 (23)
	75% - <90% **(%)**	5 (8)	12 (17)	4 (8)	12 (20)
	50% - <75% **(%)**	10 (15)	9 (13)	7 (13)	9 (15)
	>0% - <50% **(%)**	7 (11)	7 (10)	5 (9)	5 (8)
	No change or any increase or lack of asthma control or withdrawal from treatment (%)	37 (56)	25 (36)	33 (62)	21 (34)
Comparison vs placebo	Odds Ratio to Placebo		2.39		3.51
	95% CI		1.25, 4.56		1.69, 7.25
	p-value		0.008		<0.001

		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	69	53	61
	50% to 100%	22 (33)	37 (54)	15 (28%)	35 (57%)
	<50%, no decrease in OCS, lack of asthma control, or withdrawal from treatment	44 (67)	32 (46)	38 (72%)	26 (43%)
Comparison vs placebo	Odds ratio to placebo		2.26		3.36
	95% CI		1.10, 4.65		1.5, 7.52
	p-value		0.027		0.003
Reduction in Daily OCS Dose to ≤5 mg, n (%)	n	66	69	53	61
	Reduction to ≤5 mg	21 (32)	37 (54)	15 (28%)	34 (56%)
	Reduction to >5 mg, lack of asthma control, or withdrawal from treatment	45 (68)	32 (46)	38 (72%)	27 (44%)
Comparison vs placebo	Odds ratio to placebo		2.45		3.23
	95% CI		1.12, 5.37		1.38, 7.57
	p-value		0.025		0.007
Total Reduction of OCS Dose, n (%)	n	66	69	53	61
	Total (100%) reduction (0 mg)	5 (8)	10 (14)	2 (4%)	10 (16%)
	OCS taken, lack of asthma control, or withdrawal from treatment	61 (92)	59 (86)	51 (96%)	51 (84%)
Comparison vs placebo	Odds ratio to placebo		1.67		4.27
	95% CI		0.49, 5.75		0.81, 22.49
	p-value		0.414		0.087
Median Percentage Reduction in Daily OCS Dose	n	66	69	53	61
	Median (%)	0.0	50.0	0.0	64.3
	95% CI of the median	-20.0, 33.3	20.0, 75.0	-50, 20	25, 75
	Median difference		-30.0		50
Comparison vs placebo	95% CI of the median difference		-66.7, 0.0		14.3, 86.9
	p-value		0.007		<0.001

Below are some factual inaccuracies within the ERG report we would like to point out and were asked to include in our response.

***Table 26**, title reads:*

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

This is incorrect and should read:

“ICERs (£/QALY) for mepolizumab vs. SoC for patients with blood eosinophil level ≥300 cells/ul in the last year and continuous or frequent treatment with oral corticosteroids (at least 4 courses in the last year) for different treatment and waning durations”.

***Table 32**, title reads:*

“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”

This table is a modification of table 3 in our ACD response, where we clearly state that the population from which these ICERs are derived is the MENSA ITT, not our proposed sub-population. This should be clarified in the title of table 32 in the ERG report by amending the title to read as follows:

“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 (MENSA, ITT population)”

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APPENDIX

Appendix A: Subject- and Clinician-Rated Overall Evaluation of Response & Other Measures

Table 16: Summary of Clinician-Rated Overall Evaluation of Response to Therapy (MENSA, ITT Population)

Visit		Number (%) of subjects		
		Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
Week 8	n	191	191	194
	1 (Significantly improved)	12 (6)	33 (17)	42 (22)
	2 (Moderately improved)	35 (18)	42 (22)	35 (18)
	3 (Mildly improved)	40 (21)	49 (26)	56 (29)
	4 (No change)	85 (45)	53 (28)	46 (24)
	5 (Mildly worse)	12 (6)	4 (2)	5 (3)
	6 (Moderately worse)	2 (1)	2 (1)	1 (<1)
	7 (Significantly worse)	0	0	0
	Missing	5 (3)	8 (4)	9 (5)
	Odds ratio to placebo		2.11	2.38
	95% CI		(1.46, 3.04)	(1.65, 3.44)
	p-value		<0.001	<0.001
Week 16	n	191	191	194
	1 (Significantly improved)	23 (12)	37 (19)	53 (27)
	2 (Moderately improved)	29 (15)	51 (27)	49 (25)
	3 (Mildly improved)	56 (29)	44 (23)	50 (26)
	4 (No change)	65 (34)	42 (22)	30 (15)
	5 (Mildly worse)	9 (5)	7 (4)	5 (3)
	6 (Moderately worse)	3 (2)	3 (2)	0
	7 (Significantly worse)	0	0	1 (<1)
	Missing	6 (3)	7 (4)	6 (3)
	Odds ratio to placebo		1.84	2.83
	95% CI		(1.28, 2.64)	(1.96, 4.08)
	p-value		<0.001	<0.001
Week 32	n	191	191	194
	1 (Significantly improved)	18 (9)	44 (23)	60 (31)
	2 (Moderately improved)	39 (20)	51 (27)	56 (29)
	3 (Mildly improved)	44 (23)	41 (21)	35 (18)
	4 (No change)	71 (37)	36 (19)	32 (16)
	5 (Mildly worse)	5 (3)	2 (1)	1 (<1)
	6 (Moderately worse)	1 (<1)	2 (1)	1 (<1)
	7 (Significantly worse)	0	1 (<1)	0
	Missing	13 (7)	14 (7)	9 (5)
	Odds ratio to placebo		2.10	3.29
	95% CI		(1.46, 3.02)	(2.28, 4.76)
	p-value		<0.001	<0.001

Table 17: Summary of Subject-Rated Overall Evaluation of Response to Therapy (MENSA, ITT Population)

Visit		Number (%) of subjects		
		Placebo N=191	Mepolizumab 75 mg IV N=191	Mepolizumab 100 mg SC N=194
Week 8	n	190	191	194
	1 (Significantly improved)	25 (13)	39 (20)	55 (28)
	2 (Moderately improved)	29 (15)	39 (20)	32 (16)
	3 (Mildly improved)	45 (24)	45 (24)	65 (34)
	4 (No change)	79 (41)	52 (27)	33 (17)
	5 (Mildly worse)	8 (4)	7 (4)	4 (2)
	6 (Moderately worse)	3 (2)	2 (1)	1 (<1)
	7 (Significantly worse)	1 (<1)	0	0
	Missing	1 (<1)	7 (4)	4 (2)
	Odds ratio to placebo		1.59	2.51
	95% CI		(1.11, 2.30)	(1.74, 3.62)
	p-value		0.012	<0.001
Week 16	n	191	191	194
	1 (Significantly improved)	35 (18)	55 (29)	62 (32)
	2 (Moderately improved)	38 (20)	50 (26)	49 (25)
	3 (Mildly improved)	48 (25)	34 (18)	52 (27)
	4 (No change)	51 (27)	35 (18)	22 (11)
	5 (Mildly worse)	9 (5)	4 (2)	2 (1)
	6 (Moderately worse)	4 (2)	5 (3)	0
	7 (Significantly worse)	2 (1)	0	1 (<1)
	Missing	4 (2)	8 (4)	6 (3)
	Odds ratio to placebo		1.71	2.23
	95% CI		(1.19, 2.64)	(1.56, 3.20)
	p-value		0.004	<0.001
Week 32	n	191	191	194
	1 (Significantly improved)	37 (19)	57 (30)	78 (40)
	2 (Moderately improved)	31 (16)	43 (23)	48 (25)
	3 (Mildly improved)	40 (21)	34 (18)	30 (15)
	4 (No change)	63 (33)	40 (21)	26 (13)
	5 (Mildly worse)	6 (3)	2 (1)	3 (2)
	6 (Moderately worse)	2 (1)	1 (<1)	0
	7 (Significantly worse)	0	1 (<1)	0
	Missing	12 (6)	13 (7)	9 (5)
	Odds ratio to placebo		1.74	2.98
	95% CI		(1.21, 2.50)	(2.06, 4.32)
	p-value		0.003	<0.001

Table 18 Mean change from baseline in additional symptom measures (MENSA ITT population)

Time Period	Mean Change from Baseline								
	Daily rescue medication Use (occasions/day)			Daily Asthma Symptom Scores (0-5)			Number of Night Time Awakenings		
	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC	Placebo	Mepolizumab 75 mg IV	Mepolizumab 100 mg SC
Baseline	1.7	1.7	1.9	1.6	1.6	1.6	0.7	0.7	0.8
Week 1-4	-0.2	-0.4	-0.4	-0.1	-0.3	-0.3	-0.2	-0.2	-0.3
Week 5-8	-0.3	-0.5	-0.5	-0.2	-0.4	-0.4	-0.3	-0.3	-0.4
Week 9-12	-0.5	-0.5	-0.6	-0.3	-0.5	-0.6	-0.3	-0.3	-0.4
Week 13-16	-0.5	-0.5	-0.7	-0.4	-0.5	-0.6	-0.3	-0.3	-0.4
Week 17-20	-0.4	-0.6	-0.7	-0.4	-0.5	-0.6	-0.3	-0.3	-0.5
Week 21-24	-0.5	-0.6	-0.8	-0.4	-0.6	-0.6	-0.3	-0.3	-0.5
Week 25-28	-0.6	-0.6	-0.7	-0.4	-0.6	-0.6	-0.3	-0.3	-0.5
Week 29-32	-0.5	-0.6	-0.7	-0.4	-0.6	-0.6	-0.3	-0.3	-0.5

Appendix B: Baseline demographics for accepted sub-population

Table 19: Baseline Characteristics for individual trials (DREAM, MENSA, SIRIUS)

		DREAM			MENSA		SIRIUS	
		GSK Proposed Population (≥300 cells/µL in the past year with ≥4 exacerbations or mOCS)			GSK Proposed Population (≥300 cells/µL in the past year with ≥4 exacerbations or mOCS)		GSK Proposed Population (≥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	Placebo	Mepo 100mg SC
Age (yrs)	**n**	55	52	157	68	176	53	61
	Mean	49.5	51.0	49.7	49.2	52.4	50.9	48.7
	SD	10.29	10.62	11.41	13.60	13.35	10.0	13.71
	Median	51.0	51.0	51.0	49.0	55.0	53.0	51.0
	Min.	23	24	15	12	12	28	16
	Max.	67	69	73	73	82	69	70
Sex	**n**	55	52	157	68	176	53	61
	Female	33 (60%)	35 (67%)	98 (62%)	36 (53%)	101 (57%)	25 (47%)	39 (64%)
	Male	22 (40%)	17 (33%)	59 (38%)	32 (47%)	75 (43%)	28 (53%)	22 (36%)
Ethnicity	**n**	55	52	157	68	176	53	61
	Hispanic or Latino	5 (9%)	4 (8%)	13 (8%)	2 (3%)	12 (7%)	2 (4%)	2 (3%)
	Not Hispanic or Latino	50 (91%)	48 (92%)	144 (92%)	66 (97%)	164 (93%)	51 (96%)	59 (97%)
Weight (kg)	**n**	55	52	157	68	176	53	61
	Mean	78.12	74.67	79.58	79.23	76.48	86.44	78.60
	SD	16.235	13.065	16.377	20.044	18.552	18.887	16.299
	Median	76.40	76.00	78.00	77.50	74.50	84.00	75.00
	Min.	53.0	45.0	45.0	45.0	45.0	57.0	47.0
	Max.	125.0	104.0	125.0	138.0	140.0	131.5	125.0
Duration of Asthma	**n**	55	52	157	68	176	53	61
	≥1 to <5 years	8 (15%)	5 (10%)	14 (9%)	11 (16%)	19 (11%)	10 (19%)	6 (10%)
	≥5 to <10 years	13 (24%)	10 (19%)	29 (18%)	10 (15%)	31 (18%)	8 (15%)	15 (25%)
	≥10 to <15 years	11 (20%)	8 (15%)	23 (15%)	9 (13%)	35 (20%)	4 (8%)	5 (8%)
	≥15 to <20 years	1 (2%)	6 (12%)	16 (10%)	9 (13%)	16 (9%)	11 (21%)	10 (16%)
	≥20 to <25 years	7 (13%)	8 (15%)	24 (15%)	5 (7%)	19 (11%)	3 (6%)	9 (15%)
	≥25 years	15 (27%)	15 (29%)	51 (32%)	24 (35%)	56 (32%)	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 (78%)	42 (81%)	129 (82%)	67 (99%)	171 (97%)		
	No	7 (13%)	3 (6%)	14 (9%)	1 (1%)	5 (3%)		
	Unknown	5 (9%)	7 (13%)	14 (9%)	0	0		
Baseline OCS daily dose (prednisolone equivalent) [2]	**n**	55	52	157	67	172	53	61
	0	20 (36%)	20 (38%)	55 (35%)	27 (40%)	82 (47%)	0	0
	>0-<15 mg/day	23 (42%)	18 (35%)	61 (39%)	28 (41%)	64 (36%)	31 (58%)	43 (70%)

	≥15 mg/day	12 (22%)	14 (27%)	41 (26%)	12 (18%)	26 (15%)	22 (42%)	18 (30%)
	n	35	32	103	40	90	53	61
	Mean	14.32	18.55	17.55	15.29	12.13	12.87	12.34
	SD	9.702	15.158	19.013	15.356	10.486	5.664	7.372
	Median	10.00	11.25	10.00	10.00	10.00	12.5	10.0
	Min.	5.0	5.0	3.0	5.0	1.0	5.0	5.0
	Max.	50.0	60.0	160.0	80.0	50.0	30.0	35.0
Total number of exacerbations	**n**	55	52	157	68	176	53	61
	<2	0	0	0	0	0	20 (38%)	21 (34%)
	2	8 (15%)	7 (13%)	23 (15%)	13 (19%)	27 (15%)	7 (13%)	7 (11%)
	3	14 (25%)	3 (6%)	23 (15%)	7 (10%)	24 (14%)	9 (17%)	8 (13%)
	4+	33 (60%)	42 (81%)	111 (71%)	48 (71%)	125 (71%)	17 (32%)	25 (41%)
	n	55	52	157	68	176	53	61
	Mean	5.44	5.81	5.17	5.35	5.09	2.81	3.34
	SD	4.590	4.415	3.666	3.582	2.924	2.632	3.473
	Median	4.00	4.00	4.00	4.0	4.0	2.00	3.00
	Min.	2.0	2.0	2.0	2.0	2.0	0	0
	Max.	26.0	25.0	25.0	19.0	21.0	12.0	16.0
Total number of exacerbations that required hospitalisation	**n**	55	52	157	68	176	53	61
	<2	48 (87%)	49 (94%)	145 (92%)	55 (81%)	156 (89%)	50 (94%)	55 (90%)
	2	3 (5%)	2 (4%)	6 (4%)	4 (6%)	13 (7%)	0	3 (5%)
	3	2 (4%)	0	4 (3%)	5 (7%)	5 (3%)	2 (4%)	1 (2%)
	4+	2 (4%)	1 (2%)	2 (1%)	4 (6%)	2 (1%)	1 (2%)	2 (3%)
Pre-bronchodilator % Predicted Normal FEV1 (%)	**n**	55	52	157	68	176	53	61
	Mean	56.5	57.6	59.2	58.7	59.0	58.6	58.3
	SD	16.89	17.90	17.77	18.85	18.57	17.61	17.24
	Median	54.9	61.7	59.7	56.2	57.4	60.4	59.5
	Min.	26	18	18	18	24	21	18
	Max.	102	94	108	109	128	93	94
Baseline Blood Eosinophils (U/mL)	**n**	55	52	157	68	174	53	61
	Geo. Mean	420	350	360	370	300	280	260
	Median	480	400	380	410	390	310	350
	Min.	0	100	0	0	0	0	0
	Max.	2300	1500	4100	3000	2200	1800	2300
Baseline Total IgE (U/mL)	**n**	55	52	157	64	163	48	56
	Geo. Mean	174.29	166.11	154.63	98.66	155.20	115.34	122.45
	Median	181.00	104.50	149.00	116.00	167.00	112.00	106.50
	Min.	1.0	13.0	5.0	2.0	1.0	1.0	22.0
	Max.	3047.0	1913.0	9130.0	11220.0	4880.0	2429.0	918.0
Baseline ACQ-5 Mean Score	**n**	54	50	153	68	171	53	61
	Mean	2.5	2.4	2.5	2.5	2.3	1.9	2.1
	SD	1.21	1.22	1.30	1.30	1.25	1.10	1.3
	Median	2.4	2.4	2.6	2.5	2.4	2.0	2.2
	Min.	0	0	0	0	0	0	0
	Max.	5	5	6	6	5	5	6
Baseline SGRQ Total Score	**n**				68	174	53	61
	Mean				51.7	49.9	43.9	50.6
	SD				19.46	18.41	18.23	17.95
	Median				52.6	51.3	43.4	54.1
	Min.				15	5	8	18
	Max.				95	90	77	98

Appendix C: Rationale for 30% reduction in exacerbations being clinically significant

- The exacerbation reduction benefit of LABA added to ICS was systematically reviewed by the independent Cochrane Airways Group [Gibson, 2007]. This meta-analysis examined 20 studies and 4312 patients who received ICS vs. ICS + LABA (similar ICS comparison) and also higher dose ICS vs. ICS + LABA (higher ICS comparison). A significant exacerbation risk reduction of 20% (0.80; 95% CI 0.73-0.89) was associated with the addition of LABA to ICS (similar ICS comparison). Similarly, a non-significant exacerbation risk reduction of 12% (0.88; 95% CI: 0.76-1.01) was associated with addition of LABA to higher doses of ICS (higher ICS comparison).

- In biologics, a meaningful exacerbation reduction in patients already receiving maximal treatment with high-dose ICS+LABA (or other controllers) was explored. In this scenario, the only approved biologic for the treatment of asthma is omalizumab. The 28 week INNOVATE study included 419 patients inadequately controlled on high dose ICS + LABA [Humbert, 2005]. The study reported a significant and clinically meaningful 26% reduction (Rate ratio [RR] = 0.74; 95% CI: 0.552-0.998) in the rate of exacerbations.

- This study was followed by a year-long study of 427 patients inadequately controlled on high dose ICS + LABA [Hanania, 2011]. This second study reported a significant and clinically meaningful 25% reduction (RR = 0.75; 95% CI: 0.61-0.92) in the rate of exacerbations with omalizumab treatment.

Appendix D: Model adaptation

The ERG amended company model for mepolizumab was received from NICE following the issuance of ACD2. To aid transparency and to help to move towards a common position, this model has been adapted using new data, as well as revising some model inputs. Revised model inputs are described in the response under the relevant section.

Four structural changes have been made to the model, which are described below:

Mortality

- An option has been included to select asthma-related mortality based on age stratified mortality figures from 2015 (see main text for input values):

Worksheet	Cell range(s)	Change
Model Summary	G33	Added "Age stratified, 2016 to drop-down menu.
Transitions	E104:X109	Implemented underlying data for age-stratified mortality including functionality for sensitivity analyses.
Transitions	J133:J138; X133:X138	Provided functionality to use the age-stratified mortality figures in the model when the appropriate setting is selected in the Model Summary worksheet.

Duration of exacerbations

- An option has been included to select the midpoint between MENSA and Lloyd 2016 for duration of exacerbations. The values inputted is literally the midpoint between the two:

Worksheet	Cell range(s)	Change
Model Summary	G28	Added "Age stratified, 2016 to drop-down menu.
Utility values	V53:V55	Provided functionality to use the midpoint value of MENSA and Lloyd (which is sourced from cells V38 to V50), when the appropriate setting is selected in the Model Summary worksheet.

Age adjusted utility

- A drop-down button has been added to the Model summary worksheet where the user can choose whether or not to include age-adjusted utility values. Off works by setting the gender weighted age adjusted values in the table in 'utility' tab to 1, all the way down.

Worksheet	Cell range(s)	Change
Model Summary	G25	Added drop-down menu to in/exclude age-adjusted utility.
Utility values	F59:G73	Added an if-statement to put the age-adjusted utility values at one when the option is selected to exclude age-adjusted

		utility values. Setting these values to one makes sure these are not taken into account in the model engine.

Continuation criteria

- Added 3 additional options to the “Implementation of continuation criteria” drop-down menu, consisting of “≥50% exacerbation reduction”, “≥30% exacerbation reduction”, and“≥1 exacerbation reduction” (not presented in response).

Worksheet	Cell range(s)	Change
Model Summary	C28	Added 3 additional continuation criteria to drop-down menu.
Transitions	E18:X20	Added exacerbation rates for patients meeting these continuation criteria.
Transitions	E25:X28	Added exacerbation rates for patients not meeting these continuation criteria.
Transitions	G30:H30	Added proportions of patients meeting continuation criteria for the newly added continuation rules.
Model Engine	BM15:BR1215	If ConCrit=2 is selected these columns always used the exacerbation rate for OCS (cell P7 on the Model Engine worksheet). This has been changed to use the corresponding exacerbation rates as described in cells BM13:BR13. Therefore, P7 has been replaced by P8 and P9 in columns BN and BO, respectively. In the same manner, T7 has been replaced by T8 and T9 in columns BQ and BR, respectively.
Throughout model	N/A	If-statements using the “ConCrit” named range have been updated to correctly reflect the newly added continuation rules. This means that “if(ConCrit>1,” has been replaced by “if(ConCrit=2,”.

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National Institute for Health and Care Excellence (NICE)
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1st September 2016

Dear Melinda and Jeremy,

Thank you for sending the clarification questions from the Evidence Review Group, ScHARR Technology Assessment Group, and the technical team at NICE on Monday 22nd August 2016, regarding the company ACD2 response for mepolizumab in severe refractory eosinophilic asthma (ID798) submitted on 5th August 2016.

Should you have any queries with the provided responses please contact Helen Starkie Camejo (helen.j.starkie-camejo@gsk.com).

Many thanks.

Kind regards,

Helen and Christoph

Dr Helen Starkie Camejo – Programme Lead, Health outcomes, Respiratory
Dr Christoph Hartmann – Senior Medical Adviser

1. **The ERG notes that the size of the population in Analysis 3 of the company's response to ACD1 differs from that of the accepted population (176 vs 159), although they are supposed to be equivalent. Both are used in the model depending on the chosen continuation criteria (176 for no worsening of exacerbations, 159 both for 30% reduction and 50% reduction). The ERG would like to know the reason of this apparent inconsistency. This seems to be linked to the inconsistency in the mean exacerbation rates calculated by the ERG for all three condition criteria. Mean exacerbation rates were calculated as a weighted average of the rates of those who met the continuation criteria and those who didn't. The calculated average should coincide with the exacerbation rate observed in COSMOS in the accepted population (the ERG is unable to confirm this as this value has not been reported by the company). The calculated exacerbation rates of 1.478, 1.445 and 1.444 for no worsening, 30% reduction, 50% reduction respectively. The ERG notes that the first figure is different to the other two.**

   Analysis 3 in the company's ACD1 response and the 'accepted population' in the ACD2 response both refer to a sub-group defined by blood eosinophils ≥300 cells/μL in the previous year and ≥4 exacerbations in the previous year or a dependency on maintenance OCS. The data source used in both responses was MENSA, and included individuals from both 75mg IV and 100mg SC treatment arms.

   The ERG has indeed identified a small inconsistency in our figures. The reason that the population size is stated as 176 in the ACD1 response and 159 in the ACD2 response is that the former includes all patients that fulfil these criteria, in MENSA, while the latter excludes patients that did not continue from MENSA into COSMOS. Thus 17 patients did not continue into COSMOS, resulting in a population size of 159.

   The difference in the calculated average exacerbation rate arises because of this change in the population size: for the original rule, we calculated the proportion continuing based on those meeting the rule in MENSA (176 subjects); in the new continuation rules, we have applied it based on the numbers of those that left MENSA and who then enrolled in COSMOS (159 subjects). This slight difference was unintentional and was a product of the analyses being conducted at different time points. For completeness, we have applied exactly the same approach as used for the exacerbation reduction rules, to the no worsening rule. We can confirm that 143 out of 159 (89.9%) met the rule and entered COSMOS, compared with using the original inputs of 157 out of 176 (89.2%). The corresponding exacerbation rates are 1.447 rather than 1.478, (similar to that calculated for the 50% and 30% reduction rules). This translates into an ICER of £32,235 compared with £31,724 per QALY gained.

   Note, throughout the rest of this response, we present the values used originally for the no worsening rule, alongside the adjusted figures (as described above).

2. **The ERG believes it would be preferable to use the mean age of the accepted population in the model instead of that of the ITT, but this value has not been reported by the company.**

   We agree that using the mean age of the accepted sub-population (51.5 years) rather than the mean age of the ITT population (50.1 years) is preferable. Adjusting the mean age from 50.1 years (in the ITT population) to 51.5 years, to reflect the accepted sub-population, results in slightly lower ICERs in the base case analyses. Using the median age in the sub-population (53.0 years) lowers the ICERs even further (Table 1).

Table 1 The effect on the ICER with variations in mean/median age in ITT and accepted sub-group population

Results		Mean Age 50.1 years (ITT) ICER (£)	Mean Age 51.5 years (sub-group) ICER (£)	Median Age 53.0 years (sub-group) ICER (£)
Original Continuation Criterion	Original approach	31,724	30,410	28,680
	Adjusted as per Q1	32,235	30,908	29,159
Revised Continuation Criteria, 50% Reduction		27,418	26,353	24,397
Revised Continuation Criteria, 30% Reduction		28,398	27,332	25,908
		ICER (£)	**ICER (£)**	**ICER (£)**
Revised Continuation Criteria, 50% Reduction, including mOCS benefit		18,418 - 23,418	17,353 – 22,353	15,397 - 20,397
Revised Continuation Criteria, 30% Reduction, including mOCS benefit		19,398 - 24,398	18,332 – 23,332	16,908 - 21,908

3. **The ERG notes that the attrition rate does impact on the ICER, contrary to the company statement, because mortality increases with age. The attrition rate used in the model was calculated from the ITT population in COSMOS. The ERG notes this could be an underestimate given that patients are prone to discontinue treatment more in clinical practice than in a trial. However, the ERG believes it might also be an overestimate, since patients in the accepted population, being a especially severe subgroup, benefit from the treatment more on average than the patients in the ITT population. The ERG would like to know the percentage of patients in the accepted population that discontinued treatment during COSMOS.**

   In the model a 10.1% attrition rate is applied annually from year 2 onwards and this figure is derived from the COSMOS ITT population (N=66/651). We agree that it would not entirely reflect the attrition rate that would be experienced in real life use for a number of reasons. However we have been able to explore the impact of variations in this value in the accepted population. The percentage of patients in the accepted population that discontinued treatment during COSMOS was 14.5% (N=23/159), but this also includes patients who fail to meet continuation criteria.

   However, to be more reflective of clinical practice, we obtained the attrition rate by restricting only to those patients who met the continuation criteria, and moved into COSMOS. In these patients the attrition rate in COSMOS was **11.5%** (N=14/122) for the 50% (reduction in rate of exacerbations) continuation criterion, and **11.9%** (16/134) for the 30% continuation criterion. The resulting ICERs utilising these attrition rates were only marginally different from the results utilising 10.1%, from the original results (Table 2).

Table 2 The effect on the ICER with variations in attrition rate

Results		Submitted attrition rate	Attrition rate	Attrition rate
		Attrition 10.1% (ITT)ICER (£)	Attrition 11.5% (sub-group) ICER (£)	Attrition 11.9% (sub-group) ICER (£)
Original Continuation Criterion	Original approach	31,724	N/A	N/A
	Adjusted as per Q1	32,235	N/A	N/A
Revised Continuation Criteria, 50% Reduction		27,418	**27,962**	N/A
Revised Continuation Criteria, 30% Reduction		28,398	N/A	**29,065**
		ICER (£)	**ICER (£)**	**ICER (£)**
Revised Continuation Criteria, 50% Reduction, including mOCS benefit		18,418 - 23,418	18,962 - 23,962	N/A
Revised Continuation Criteria, 30% Reduction, including mOCS benefit		19,398 - 24,398	N/A	20,065 - 25,065

When applying both the adjustment to mean age (as per Q2) and attrition rates, the resulting ICERs are lower than the originally submitted ACD2 response values (see Table 3 below).

Table 3 The effect on the ICER with variations in mean age and attrition rate

Results		Mean Age 50.1 years; Attrition 10.1% (ITT) ICER (£)	Mean Age 51.5 years; Attrition 11.5% (sub-group) ICER (£)	Mean Age 51.5 years; Attrition 11.9% (sub-group) ICER (£)
Original Continuation Criterion	Original approach	31,724	N/A	N/A
	Adjusted as per Q1	32,235	N/A	N/A
Revised Continuation Criteria, 50% Reduction		27,418	**26,897**	N/A
Revised Continuation Criteria, 30% Reduction		28,398	N/A	**27,937**
		ICER (£)	**ICER (£)**	**ICER (£)**
Revised Continuation Criteria, 50% Reduction, including mOCS benefit		18,418 - 23,418	17,897 – 22,897	N/A
Revised Continuation Criteria, 30% Reduction, including mOCS benefit		19,398 - 24,398	N/A	18,937 – 23,937

They [ERG] have also raised a few concerns which we felt would be valuable to share in advance of their formal critique

4. **The proposed continuation criteria consists of an exacerbation reduction or a reduction in OCS use while receiving mepolizumab for 12 months. The trial used to inform the model (MENSA) does not include a subgroup with OCS reduction and therefore the ERG thinks the model cannot be used to provide an estimate of the ICER for people who have a reduction in OCS use only. The ERG believes that the ICER for the subgroup of patients that achieve OCS reduction but do not achieve exacerbation reduction would be much higher than that of patients who do achieve an exacerbation reduction. The best estimate for this subgroup may be the one based**

on the population of SIRIUS (the OCS reduction trial), but this would produce a favourable ICER to mepolizumab, as some of these patients also had significant reduction in exacerbations.

We acknowledge that it is difficult to use the model to provide an estimate of the ICER for people who have a reduction in OCS use only. As explained in our response to the ACD2, in MENSA, patients were not allowed to reduce their mOCS dose during the trial and therefore it is not possible to assess whether or not they would have been able to reduce their OCS dose. For this reason we applied the exacerbation critera to the total population including those patients on mOCS. We acknowledge that within the model, the resulting ICER for those patients on mOCS but who do not experience a reduction in exacerbations may be higher. However, as discussed in our submission and as acknowledged by the committee, we are not able to, due to lack of evidence, ascribe a meaningful utility benefit to the reduction in mOCS dose despite it being clear that this has significant clinical benefit that is highly valued by clinicians and patients.

We do not believe that using SIRIUS would necessarily help in understanding this further. SIRIUS was a study specifically designed to assess the steroid sparing effectiveness of mepolizumab. Therefore whilst it may be possible to apply the continuation criterion with respect to mOCS use it may not fully reflect the effectiveness benefit from exacerbation reduction that these patients would receive. Additionally, EQ-5D data were not collected in SIRIUS and therefore the EQ-5D benefit associated with a reduction in OCS dose cannot be evaluated.

Whilst we accept that this does provide some uncertainty we would draw the ERG's attention to the results of our original continuation criteria that allowed all patients to continue who did not worsen on treatment (i.e. did not apply either a 30 or 50% reduction) and in this scenairo an ICER of £30,908 utilising the mean age 51.5 years and the approach as per Q1, was obtained. These estimates also do not take into account the benefit of reducing mOCS exposure and so the most plausible ICER utilising either the 30 or 50% criterion is still likely to lie significantly below the £30,000 threshold.

5. **The ERG is surprised by the new baseline EQ-5D values reported by the company. The ERG notes that the fact that the mean EQ-5D score is higher in the accepted population (4 or more exacerbations in the previous year or on mOCS) than in the ITT population in the placebo arm is counter-intuitive, since the accepted population is supposed to be a severe subgroup of the ITT population. The description provided by the company of the methodology used to calculate the baseline adjustment appears correct, however, the ERG cannot validate it given that it has not access to individual patient data. The ERG notes that baseline adjustment of EQ-5D scores has a large impact in the ICER.**

We acknowledge the point raised by the ERG with regards to EQ-5D values being higher in the accepted population compared to the ITT population. Table 4 presents the unadjusted, observed EQ-5D values, as well as the adjusted values, in the ITT and accepted population. It shows, in line with the ERGs concerns, that the EQ-5D values in the accepted population are higher than in the ITT population. We acknowledge that it may not be intuitive that the values are worse in the ITT, however as we have previously described there are limitations in the use of EQ-5D in the severe asthma population, with 30% of patients in DREAM reporting perfect health at baseline, and this may also be reflected in these reported values.

Table 4 Summary of observed and adjusted baseline EQ-5D values in the ITT population and Accepted population, DREAM

		DREAM					
		ITT Population			≥300 cells/μL in the past year with ≥4 exacerbations or mOCS		
	Analysis	Placebo	Mepo 75mg IV	Total	Placebo	Mepo 75mg IV	Total
Observed baseline EQ-5D Score	**n**	155	153	308	55	52	107
	Mean (SE)	0.743 (0.015)	0.717 (0.017)	0.730 (0.011)	0.794 (0.024)	0.716 (0.034)	0.756 (0.021)
Adjusted baseline EQ-5D	**Mean**	0.727	0.727	0.727	0.747	0.747	0.747

It is worth noting that using SGRQ, a more sensitive asthma specific quality of life measure in the MENSA trial, a more intuitive trend in the accepted population compared to the ITT population was observed (Table 5). The SGRQ values for the accepted population indicated a more severe health burden compared to the ITT population. This further highlights that SGRQ is a more appropriate HRQoL tool for capturing QoL in this severe asthma population.

Table 5 Summary of SGRQ values in the ITT population and Accepted population, MENSA

		MENSA				
		ITT Population			≥300 cells/μL in the past year with ≥4 exacerbations or mOCS	
Characteristic	**Analysis**	Placebo	Mepo 75mg IV	Mepo 100mg SC	Placebo	Mepo 75mg IV/100mg SC
Baseline SGRQ Total Score	**n**	190	190	193	68	174
	Mean	46.9	44.4	47.9	51.7	49.9
	Median	46.1	45.5	48.6	52.6	51.3

We are unable to provide IPD data for the ERG to validate our statistical adjustment of the EQ-5D values. However we would like to reassure the ERG that these analyses were carried out by our statistical departments who operate to our defined standard operating processes including quality control, consistent with those utilised for our regulatory activities. The analysis was performed by one statistician and independently replicated by another.

Asthma UK response to NICE's second appraisal consultation document on mepolizumab for treating severe refractory eosinophilic asthma

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

Asthma UK considers mepolizumab to be a novel and innovative treatment that seeks to address an unmet need for people with severe eosinophilic asthma. While we appreciate that NICE has accepted some of the points we submitted in response to the first appraisal consultation document (ACD) around the target population for mepolizumab, some key considerations remain unaddressed and therefore many of the areas of concern are unchanged from our previous submissions – in particular around oral corticosteroid (OCS) use.

The Committee heard from one patient expert on the serious reality of living with severe asthma. Another we have worked with describes their experience of the condition in clear terms:

"On a bad day I feel like I'm drowning and I can't reach the surface of the water and I'm going to burst, yet a tiny, tiny bit of air keeps me alive. It's very scary – I feel like I'm living with a time bomb and if I have a bad attack I say to myself 'Is this the one that will kill me?'"

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 OCS, are often very serious. We were disappointed that a study by Sweeney et al. did not appear to be considered in relation to comorbidities resulting from severe asthma requiring systemic corticosteroid therapy (http://dx.doi.org/10.1136/thoraxjnl-2015-207630). This is a recent study, published online earlier this year, which presents data from two large severe asthma populations (the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry) and shows that OCS use results in a higher prevalence of comorbidities - including type II diabetes, hypertension and osteoporosis.

The committee has again recognised that some benefits related to avoiding the significant adverse effects of OCS use had not been fully captured in the QALY measure (4.28). There is a significant gap in high quality data that considers the morbidity due to OCS use in people with severe asthma, but this should not mean that NICE cannot consider the evidence that is available. The Sweeney et al. paper has been described as "the best estimate yet of the burden of OCS treatment in severe asthma" (Choo & Pavord 2016, http://thorax.bmj.com/content/71/4/302.full). We were therefore disappointed that this was not included in the assessment of mepolizumab – this should be reconsidered by the committee and factored into the incremental cost-effectiveness ratio (ICER), in addition to quality-of-life benefits to carers. We note that this point was also made by both the manufacturer and British Thoracic Society in their responses to the ACD.

Estimating the impact of the effects of OCS use is a crucial area that needs to be addressed, particularly given that from a patient perspective, reduced use is a key benefit of any future treatment. Mepolizumab is the first in what we anticipate will be a next generation of treatments for people with severe eosinophilic asthma. Unless the true

impact of OCS use is captured, we are concerned that similar novel and innovative treatments for severe asthma will not be comprehensively assessed.

One patient wrote to Asthma UK recently to give us an insight on how mepolizumab had improved their day-to-day life. His asthma meant that he would be totally out of breath after a short walk, light-headed, and gasping for breath. After taking part in one of the trials for mepolizumab in Southampton he was able to act as a sole carer to his wife over several years before her death – in his words, he "could not have done this without the aid of the drug." Every effort should be made to ensure this is made available to patients. Whilst this is only one example Asthma UK believes this brings to the fore the lived experience of severe asthma and the impact that it has on people's quality of life and the role that they are able to play in society through work and family life. Innovative new treatments that enable people to play a greater role, live more independently and enable people to do more through employment and in family life are urgently needed for this cohort.

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

We note that the committee has remained unchanged on the issue of how to capture the health-related quality-of-life benefits of mepolizumab in its model. Clinicians we consulted as part of our response to the first ACD agreed that the St George's Respiratory Questionnaire (SGRQ) was a more appropriate method than EQ-5D for measuring improvements in quality of life for people with severe asthma due to it being able to effectively capture exacerbations.

As highlighted by the manufacturer, in the DREAM study, a third of patients reported "perfect health" on the EQ-5D at baseline. Severe asthma is a condition where between attacks patients can be considered well in between exacerbations of their condition. However, quality of life is severely impaired during attacks and, in many patients with severe eosinophilic asthma, by the treatment required to treat and prevent these attacks.

EQ-5D is effective in capturing some measures of patients' health-related quality of life, but often these are not key issues for people with severe asthma. In contrast, SGRQ focuses more on capturing the quality of life measures of primary concern to people with a severe respiratory condition - measuring symptom-control (such as cough, wheeze, breathlessness, frequency of attacks), activity (focusing on limitations due to breathlessness), and impact (which includes a range of factors including side effects of prescribed medication). Similarly we would not expect these factors of concern to people with severe asthma to be applicable to a number of non-respiratory conditions. NICE has to appreciate that in relying on EQ-5D measures it is missing the true impact this treatment has on severe asthma.

We do not believe that "perfect health", as captured in EQ-5D, is a true starting point for people with severe asthma, as they 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 – their baseline for what constitutes good health will naturally be set at a lower level for a condition they have had to manage throughout their lives. If the EQ-5D model is unable to capture

improvements in quality of life in a third of the population modelled, this highlights the need for a more appropriate model. We urge NICE to reconsider using data from SGRQ in its model to help to fully capture the benefits from this treatment, which we believe are significant. For example, the MENSA study of mepolizumab showed that the baseline scores on the SGRQ in those with severe eosinophilic asthma were equivalent to those seen in patients with severe COPD (Ortega et al. 2014, http://www.nejm.org/doi/full/10.1056/NEJMoa1403290). Treatment with mepolizumab was associated with a 10 point improvement in SGRQ in the population accepted as being potentially eligible for treatment based on the latest ACD. The improvement in this measure is roughly 3 times more than has been found for Seretide vs placebo in severe COPD (Calverley et al. 2007, http://www.nejm.org/doi/full/10.1056/NEJMoa063070).

We appreciate that the committee has considered two separate models on which to model age-related mortality. While Roberts et al. may look at a larger population and a broader range through its age stratification, it is likely to underestimate the number of deaths due to it not including comorbidities. In contrast, Watson et al. includes deaths from all causes after hospitalisation for asthma, so including this in the ICER model is more likely to capture mortality from comorbidities and give a more accurate picture of asthma mortality.

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

Asthma UK remains deeply disappointed in the draft recommendation, and is extremely concerned that the ICER still fails to take key considerations into account relating to asthma. Mepolizumab is an innovative treatment which meets an unmet need for severe eosinophilic asthma and has shown significant clinical benefit in clinical trials. We strongly urge the appraisal committee to reconsider this draft decision.

NICE must find a way to take into account the impact on improving the lives of carers, and the health and quality of life benefits of reducing OCS, which as highlighted by the appraisal committee would reduce the ICER.

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.

Additional comments on the ACD

None

NHS England Response to NICE ACD – Mepolizumab for treating severe refractory eosinophilic asthma

Please find NHS England's response to the ACD – Mepolizumab for treating severe refractory eosinophilic asthma which has been reviewed by the Specialised Respiratory Services (adult) CRG

Has all of the relevant evidence been taken into account?
No. The most recent publication examining treatment response to mepolizumab stratified by baseline eosinophil thresholds has not been included. Ortega et al. Lancet Respir Med 2016, epub.
Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
The summary of clinical effectiveness is a reasonable interpretation of the evidence. The summary of cost effectiveness is an incomplete interpretation of the evidence. For instance: 4.17 – not responding to mepolizumab does not indicate more severe disease; 4.21 there is no evidence to support the hypothesis that there will be a weaning of treatment effect over time. Importantly the statements provided in 4.23 are incorrect. The committee are not justified in concluding that an on treatment utility gain was inappropriate given that in patients with a baseline blood eosinophil count of 300 mepolizumab produced a 10.4 point improvement in SGRQ and 0.49 improvement in ACQ-5. These symptomatic improvements cannot be explained solely on the basis of a decrease in exacerbation frequency. The committee should have modelled an appropriate stopping rule to examine its impact on the ICER per QALY.
Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
No. The committee has not taken into account all of the evidence and has in part incorrectly interpreted the underlying pathophysiology of the disease when producing its modelling assumptions. Further work is required with regards both the addition of a stopping rule and the impact of the improvement in on treatment utility gain on the ICER per QALY.
Any other comments
None

NOVARTIS

Mr M Boysen
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28th June 2016

Dear Mr Boysen,

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

Thank you for your letter dated 1st June 2016 inviting comments on the above Appraisal Consultation Document (ACD), in which omalizumab (manufactured by Novartis) is mentioned.

In addition to our comments in response to the 1st ACD consultation we have 2 further comments, please find these summarised below:

1. Novartis believes that information regarding oral corticosteroid use should reflect the data that was presented for analysis and discussed at the committee meeting (changes in italic and underlined, section 4.7, page 30). Additionally, we believe the term 'maintenance' oral corticosteroid is ambiguous and subject to interpretation and greater clarity should be provided.

   The current text states:
   The committee noted that the company presented new analyses for 3 further populations after consultation (see section 3.48), with analysis 3 put forward as the company's preferred population. The committee noted that this included patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year, and a blood eosinophil count of 300 cells/microlitre or more per year. Having considered all the comments, the committee concluded that the population in analysis 3, that is, people with a blood eosinophil count of 300 cells/microlitre or more per year and at least one of the following:
   - 4 or more exacerbations in the previous year
   - on maintenance oral corticosteroids

   would best reflect the population seen in UK clinical practice.

   However, analysis 3 that was presented at the 2nd Appraisal Committee meeting included patients with an eosinophil count of 300 cells/microlitre in the last year AND continuous or frequent (≥4) treatment with oral corticosteroids in the last year. Therefore, we believe that this section should reflect the population included in the analysis and highlight the following suggested amends (italics and underlined):

   The committee noted that the company presented new analyses for 3 further populations after consultation (see section 3.48), with analysis 3 put forward as the company's preferred population. The committee noted that this included patients on *continuous or frequent* oral corticosteroids and/or 4 or more exacerbations in the previous year, and a blood eosinophil count of 300cells/microlitre or more per year. Having considered all the

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comments, the committee concluded that the population in analysis 3, that is, people with a blood eosinophil count of 300 cells/microlitre or more per year and at least one of the following:

- 4 or more exacerbations in the previous year
- on *continuous or frequent (≥4) courses* of oral corticosteroids *in the previous year*

would best reflect the population seen in UK clinical practice.

2. The following statement should be corrected to state omalizumab instead of mepolizumab (italics and underlined, section 4.11, pg 32)

   During its first meeting, the committee noted that the company had presented no data for using mepolizumab after omalizumab. After consultation, the company clarified that a small number of patients in the MENSA trial were previously treated with *omalizumab* (with an interval of 130 days) and that the efficacy was comparable to omalizumab-naïve patients in the subcutaneous 100-mg group.

Please do not hesitate to contact me if you require any further information.

Yours sincerely,

V. Hacking

Victoria Hacking

Health Economics & Outcomes Research Manager
Novartis Pharmaceuticals UK Ltd.

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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

Jeremy Powell
Project Manager
NICE

Dear Jeremy

Re: Single Technology Appraisal (STA)
Mepolizumab for treating severe eosinophilic asthma (ID798)
Consultation June 2016

Thank you for asking me to comment on the second appraisal consultation document for mepolizumab published in June 2016. I agree with the preferred population stated as asthmatics on step 4 or 5 of the BTS guidelines with a peripheral blood eosinophil count of ≥300 cell/microlitre in the previous year and 4 or more exacerbations or who are on maintenance oral steroids. I have three minor caveats:

1. The document suggests that there needs to be a blood eosinophil count of ≥300 cell/microlitre in the previous year, but the term used is '≥300 cell/microlitre **per year'**. This is not a phrase generally used to describe a blood eosinophil count and will be confusing to physicians prescribing the medication. The phrase '≥300 cell/microlitre **in the previous year (or previous 12 months)'** is better.

2. Exacerbations need to be qualified as 'severe exacerbations requiring a course of oral corticosteroids'

3. It is important that objective evidence of adherence/compliance is emphasised in the guidance

A further minor point not relevant to the description of the preferred population is that the guidance states on page 27 that the clinical experts could not offer a specific definition of the term refractory

asthma. In fact we did offer such a definition taken from a consensus paper produced by the American Thoracic Society (1). It is just that this is not routinely used in clinical practice.

1. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. Am J Respir Crit Care Med. 2000;162(6):2341-51.

I hope these comments are helpful

with kind regards

Andy Wardlaw

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

Name	[redacted]
Role	NHS Professional
Other role	Consultant Respiratory Physician
Organisation	British Thoracic Society Severe Asthma Network
Location	England
Conflict	Some of the signatories have participated in phase III studies with mepolizumab and their institutions will have received renumeration from Glaxo SmithKline for participation in these studies. Some will have received renumeration from attending advisory boards and/or speaker fees from GSK. A full list of DOI is available on request.

Comments on the ACD:

As clinicians looking after patients with severe asthma in the UK, we would like to comment on this NICE ACD. We are pleased that the committee is persuaded of the clinical effectiveness of this first in class novel therapy for patients with severe eosinophilic asthma.

Once again we strongly disagree with the draft recommendation that mepolizumab is not recommended as an add-on for treating severe refractory eosinophilic asthma. There are consistent flaws within the committee's assumptions that are based on an incomplete understanding of both the underlying pathology and clinical reality of patients with severe asthma. We would strongly recommend that the committee seeks external expert input at their next meeting.

Cost effectiveness

The proposed population of patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year with a blood eosinophil count of 300 cells/microlitre in the previous 12 months is logical and consistent with the patient population that we would wish to treat.

3.50 " Not including a utility gain for treatment with mepolizumab over and above the gain from a reduction in exacerbations is illogical. Ortega et al, Lancet Resp Med 2016, epub clearly demonstrates an improvement in patients with eosinophils of 300 or higher of 10.4 in SGRQ and 0.49 in ACQ-5. It is highly unlikely that a 59% reduction in annual exacerbation rate produces such a significant effect in these two patient reported outcome measures.

Clearly the addition of a stopping rule would have a significant impact on the ICER per QALY. Based on the available evidence and expert clinical opinion we would suggest that mepolizumab is continued after 12 months if there has been a 50% reduction in exacerbation frequency and/or a 50% reduction in oral corticosteroid dose.

Committee discussion

4.17 The concept that patients who do not respond to mepolizumab are more likely to have severe disease than patients who do respond has no immunological or clinical

plausibility and should be removed. Patients with T2 high driven inflammation may be IL-5 or IL-13 predominant and it does not follow that a lack of response to blocking a single pathway indicates increased disease severity.

4.18 For the reasons stated above the ERG's analysis is not more plausible.

4.21 There is no reason to suspect a waning of treatment effect. Patients have been successfully treated with omalizumab for over 10 years with no waning of the effect.

4.22 The unlicensed dose of mepolizumab used in DREAM was 75mg intravenously.

Conclusion

We agree that the currently defined patient population is the correct one to be applied to clinical practice and have included a stopping rule that we would be happy to apply to our carefully selected patient cohorts.

We are concerned that incorrect assumptions made by the ERG are inflating the ICER per QALY and urge the committee to invite experts in severe asthma to attend the third appraisal committee meeting to help interpret the evidence base correctly.

[redacted]

Name	[redacted]
Role	Carer
Location	
Conflict	
Comments on the ACD:	
I am writing this email to you in hope that it will get to the correct department that deals with the above new drug for severe asthma. Please could some one explain to me why you do the trials in England giving hope to hundreds of people then take away that one last hope by making it just out of reach . My daughter [redacted] has been asthmatic since the age of eleven and has spent over half of her life in and out of hospital with eosinophilic asthma that is as yet been treatable with anything other than the standard asthma medication . In 2011 she was asked to participate into mepolizumab trial and she was lucky enough to have been on the middle dose and not a placebo . And for the time in 20 years this drug actually helped her and for that 12 months of the trial she didn't have one episode of exacerbation of her asthma and finally felt that there was hope for her to have some kind of near normal life , that now has been taken away because the nice has recommended that it is not used on the nhs . I would just like to point out that all the medication that my daughter is on at the moment (2 steroid inhaler 500mg 2 puffs twice a day 1 ventolin inhaler 2 - 8 puffs every 4 - 6 hours 1 atrovent inhaler 2 puffs 3 times a day a base dose of 10mg of prednisone daily only the last 3 months that has gone up to 50mg and is at present 25mg daily 2 tablets of 250mg of aminophyline twice a day and at least one visit to a&e a week some times 2 visits the cost of all of this per year far out weighs the cost for her to have the mepolizumab injection once a month . Why is it not available in the uk but is available in the US and the European Union . I would be grateful if some one could explain this to me . Thank you for taking the time to read this and I hopefully look forward to hearing from you .	

Mepolizumab for treating severe eosinophilic asthma: A Single Technology Appraisal

ERG's critique of the company's response to the ACD2

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	Date completed (11/09/2016)

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Executive summary

In response to the second Appraisal Committee Determination (ACD2), the company presented new evidence and a new Patient Access Scheme (PAS) price for mepolizumab. The company presented the results of new analyses based on the new price, new evidence and some alternative assumptions to those favoured by the Appraisal Committee (AC).

The population used in the analyses, denoted the 'accepted population', was that which the AC concluded would best reflect the population seen in UK clinical practice, that is, patients with blood eosinophil count of 300 cells/μL or more per year and at least one of the following:

- 4 or more exacerbations in the previous year
- on maintenance oral corticosteroids (mOCS).

Following the AC's conclusion that continuation criteria (CC) linked to improvement would have been more appropriate, the company presented analyses based on different CC. As alternatives to the original criterion, that is, that patients do not experience a worsening in the exacerbation frequency from baseline, the company proposed the following continuation criteria:

- a 50% (or 30%) reduction in the number of exacerbations compared with the previous year OR
- a reduction in mOCS dose while maintaining asthma control

For their new analyses the company deviated from some of the AC's preferred assumptions, as described in Table 1.

Table 1: Assumptions used by the company different to those accepted by the AC

	AC's preferred assumption	**Company's assumption**
Duration of the disutility caused by exacerbation	Use MENSA mean durations of exacerbations	Use midpoint between Lloyd *et al.* and MENSA
Treatment-dependent utilities	No utility gain obtained for mepolizumab treatment on top of exacerbations	Different utilities based on DREAM for on and off treatment
Age-adjustment of utilities	Yes	No

The base case incremental cost-effectiveness ratios (ICERs) of mepolizumab compared with standard of care (SoC) for the different CC presented by the company are provided in Table 2. In the scenario analyses conducted by the company, the ICERs ranged between: £23,212 and £32,475 per QALY gained for the original CC (no worsening in exacerbation rate); between £23,193 and £29,828 for the 30% reduction in exacerbations CC; and between £21,275 and £28,134 for the 50% reduction CC. The ERG notes that the main drivers of the change in the ICER of mepolizumab versus SoC

compared with those presented in the ACD2 are: the new proposed PAS price; using different EQ-5D utilities for on and off treatment; and, baseline adjustment of EQ-5D scores in the accepted population.

The ERG notes that the efficacy data (exacerbation rates and utilities) used in the model are based on studies where mOCS dose reduction was not allowed. Therefore, the ERG notes that the ICERs reported by the company, and the ERG, are only representative of patients whose mOCS dose is not reduced during treatment.

The ERG conducted additional analyses applying the AC's preferred assumptions to the company's revised model whilst including new evidence presented by the company. The base case ICERs for the AC's preferred assumptions calculated by the ERG are considerably higher than those of the company's base case (see Table 2). The ERG notes that the main drivers of the change in the ICER are: assuming that mepolizumab does not give a utility benefit over and above that associated with reduced exacerbations; and adjusting for the baseline imbalance in EQ-5D scores in the accepted population. The ERG also performed exploratory analyses based on some of the alternative assumptions favoured by the company, new evidence provided by the company during the clarification round and additional corrections to the model. The ERG provides its most plausible ICER based on the available evidence – from here on termed as the ERG's most plausible base case. The ERG notes that these ICERs are slightly higher than those of the company's.

Table 2: Summarised base case ICERs (£/QALY) for mepolizumab vs. SoC

	Company's base case	AC's preferred base case + new evidence	ERG's most plausible base case
No worsening (original CC)	£32,235	£48,084	£31,895
30% exacerbation reduction	£28,398	£49,376	£31,378
50% exacerbation reduction	£27,418	£45,831	£29,163

Scenario analyses undertaken by the ERG indicated that assuming a lower age of start of treatment produced results considerably less favourable for mepolizumab versus SoC, as was the case when it was assumed that the efficacy of mepolizumab waned over time. In contrast, assuming a lower attrition made the results more favourable for mepolizumab versus SoC.

The ERG notes that the ICERs in Table 2 are appropriate only when applying continuation criteria for exacerbation rates. The ERG believes that an ICER relating to patients who only met the second continuation criterion proposed by the company (a reduction in mOCS dose while maintaining asthma control) could not be robustly calculated from data available to the ERG. The ERG therefore performed approximate threshold analyses for this subgroup where it was assumed that mepolizumab

did not reduce the exacerbation rates and that any cost offsets were ignored. Based on the AC's preferred assumptions, the ERG concluded that the utility accounting for the mOCS reduction benefit [redacted] for the ICER of mepolizumab versus SoC to be under £30,000/QALY gained. Based on the ERG's most plausible base case, which included the company's baseline adjusted EQ-5D values, the ERG calculated that the ICER of mepolizumab would be £60,825 excluding exacerbation reduction benefits and that mOCS reduction would have to result in additional [redacted] QALYs [redacted] for the ICER of mepolizumab versus SoC to be under £30,000 per QALY gained. The ERG notes that the ICER for a CC that includes exacerbation reduction or mOCS dose reduction should be calculated as the average of the ICERs for the two subgroups of patients that meet each continuation criterion, weighted by the proportion of patients in each subgroup. The ERG notes that this could produce ICERs significantly higher than those estimated in this report and in the company's submission, which are based on only patients who met the different exacerbation reduction criteria.

1 Critique of the new evidence presented by the company

Following the publication of the second Appraisal Consultation Document (ACD2) the company has provided, in agreement with NICE, new clinical and cost effectiveness evidence. The new submission included a new version of the model, based on the one used by the Evidence Review Group (ERG) in the critique to the company's response to the first Appraisal Consultation Document (ACD). The company has also offered a new Patient Access Scheme (PAS) price of [redacted] per 100 mg vial of mepolizumab.

The company used in their analyses the population believed by the Appraisal Committee (AC) to best reflect the population seen in UK clinical practice (referred to as "accepted population"): patients with a blood eosinophil count of 300 cells/μL or more per year and at least one of the following:

- 4 or more exacerbations in the previous year
- on maintenance oral corticosteroids (mOCS).

1.1 Duration of disutility from exacerbations

The ERG acknowledged in its response to the first ACD that there is potential for the duration of the disutility from exacerbations to be underestimated using only the average length of exacerbations in MENSA. The ERG acknowledged that, as claimed by the company, the disutility due to exacerbation could last longer than the length of the OCS burst. The company decided to use the midpoint between the mean duration of exacerbations in MENSA and the length of the Lloyd *et al.*[1] study as a compromise. The ERG notes that adopting the midpoint between MENSA and Lloyd *et al.*[1] instead of MENSA reduces slightly the ICER of mepolizumab versus SoC.

1.2 Utilities on and off treatment

The ACD2 reflects that the AC concluded that an on-treatment utility gain was inappropriate, based on feedback from clinical experts that mepolizumab was unlikely to have an effect on symptoms. The company argues in their response to ACD2 that this is not the case and refers to the ERG report as well as to experts' responses to the first ACD. The company also claims that mepolizumab reduces eosinophilic inflammation which results in improved symptom control, quality of life and lung function, in addition to reducing the risk of exacerbations. In addition to these arguments, the company presented Asthma Control Questionnaire (ACQ) and St. George's Respiratory Questionnaire (SGRQ) data for the accepted population and analysed the SGRQ data to show the benefit of mepolizumab over and above the benefit experienced from a reduction in exacerbations. The analysis of SGRQ data was twofold. The first part attempted to adjust the change in SGRQ scores for changes in exacerbations from baseline. The ERG agrees that this analysis indicates that patients with the same

change in exacerbation rate (e.g. either a 0, 1, 2 or ≥3 reduction) show a greater SGRQ improvement in the mepolizumab group than in the SoC group. The second part attempted to prove that the frequency of respiratory symptoms domain was the key driver of the change in SGRQ score. The company also referred to the statistically significant difference in the overall evaluation of treatment response rated by subjects and clinicians while blinded to treatment. However, the ERG notes that these differences could also be confounded by the improvement in exacerbation reduction.

1.3 Baseline adjusted EQ-5D scores

The company identified a significant difference in mean baseline EQ-5D scores between the mepolizumab (0.716) and standard of care (SoC) (0.794) arms in the accepted population. The company argued that the baseline imbalance led to an underestimation of the improvement in EQ-5D scores in patients on mepolizumab compared with SoC. The company calculated baseline-adjusted EQ-5D scores using least squares means from a mixed model of repeated measures with covariates of treatment, age, visit, baseline and interaction between treatment and visit and visit and baseline EQ-5D scores. The results of the baseline adjustment of EQ-5D scores are shown in Table 3.

Table 3: Baseline adjusted and unadjusted EQ-5D scores, mean (standard error), DREAM, Accepted Population

	Baseline EQ-5D score	End of trial*	
		Unadjusted EQ-5D score	Adjusted EQ-5D score
SoC	0.794 (0.024)	0.792 (0.026)	0.765 (0.020)
Mepolizumab (75mg IV)	0.716 (0.034)	0.797 (0.023)	0.804 (0.020)
Difference mepolizumab vs SoC	-0.078	0.005	0.039

*Used in the model

The ERG notes that the description provided by the company of the methodology used to calculate the baseline adjustment appears correct, however, the ERG could not validate these results given that it has not access to individual patient data. The ERG was surprised by the baseline EQ-5D mean scores reported by the company for the accepted population. The ERG notes that the accepted population is a severe subgroup of the intention-to-treat (ITT) population of DREAM at baseline. However, the mean EQ-5D score for the ITT population in SoC arm reported in the DREAM clinical study report[2] was noticeably lower (0.743) than that reported for the accepted population (0.794): the ERG would have expected that patients in the accepted population, would have a lower mean EQ-5D score at baseline than the ITT population. The changes from baseline are also of a different direction in the placebo arm for the ITT population (0.07) and the accepted population (-0.002). The ERG observed that a baseline imbalance was present too in the original GSK proposed population, patients with ≥150 cells/μL baseline blood eosinophils and ≥4 exacerbations in past year or mOCS use (SoC: 0.80; mepolizumab:

0.73). However, no such imbalance was observed in the GSK restricted population, patients with ≥150 cells/μL baseline blood eosinophils and ≥4 exacerbations in past year (0.78 vs 0.77). Utility data relating to patients with ≥300 cells/μL baseline blood eosinophils and ≥4 exacerbations in past year were not provided by the company (although it is acknowledged that the company had not been asked for these data).

The ERG shared these concerns with the company via NICE. The company acknowledged in its response[3] that "it may not be intuitive" but attributed it to the alleged limitations of the EQ-5D tool to capture health-related quality of life in the severe asthma population. The ERG notes the volatility of the baseline imbalance across subgroups and assessed the impact of excluding the baseline adjustment in its exploratory analyses.

During the consideration of the new evidence, the ERG realised that it is not appropriate to apply the utility score of patients on SoC to patients that stopped mepolizumab treatment after failure to meet the CC or who met the CC but discontinued treatment later on. Following the same logic as for exacerbation rates, described in a previous document,[4] patients not meeting the CC should be assigned a utility score such that the average of the utility scores for patients meeting the CC and those not meeting the CC, weighted by the percentage in each group, would equal the average utility score for all patients on mepolizumab, that is:

Utility all patients = % met CC * Utility met CC + (1 -% met CC) * Utility not met CC

Therefore:

Utility not met CC = (Utility all patients - % met CC * Utility met CC) / (1 -% met CC)

It is to be expected that patients not meeting the CC will be a more severe subgroup of patients and therefore their utility score will be lower than the average utility score of patients on SoC.

Similarly, the utility of mepolizumab discontinuers (patients that met the CC but discontinued mepolizumab at a later stage) will have a higher utility than the average utility of patients on SoC. The ERG calculated the utilities for the mepolizumab discontinuers so that the average utility of patients who did not meet the CC and the utility of those discontinuing mepolizumab weighted by the percentage of patients meeting the CC would equal the average utility in the SoC group, that is:

Utility SoC = % met CC * Utility discontinuers + (1 -% met CC) * Utility not met CC

Therefore:

Utility discontinuers = (Utility SoC – (1-% met CC) * Utility not met CC) / % met CC

Table 4 shows the different EQ-5D scores calculated for patients in the different states in the mepolizumab as used in the ERG's exploratory analyses.

Table 4: EQ-5D utilities for patients in different states in the mepolizumab arm.

	Patients meting CC (%)	EQ-5D scores			
		All patients	Patients meeting CC	Patients not meeting CC†	Mepolizumab discontinuers†
Original CC: no worsening of exacerbations	89.9‡	0.804	0.806	0.765*	0.765*
Revised CC: 30% reduction	84.3		0.824	0.697	0.778
Revised CC: 50% reduction	76.7		0.823	0.741	0.772

†Calculated by the ERG (in the company's base case these values were the same as SoC (0.765) regardless of CC). Example of calculation: utility for patients not meeting the CC of 30% reduction: (0.804 - 0.843*0.824) / (1-0.843) =0.697

‡Percentage updated in the clarification response as explained in Section 0

*Capped to the SoC score (0.765) because it is assumed patients discontinuing mepolizumab cannot have a quality of life higher than SoC. This affects patients not meeting CC as well as discontinuers

1.4 Age-adjusted utilities

The company disagreed with the ERG and the AC on the appropriateness of adjusting utilities for age. To support their claim that utility is not reduced in older cohorts, the company presented a table of mean EQ-5D scores (both adjusted and unadjusted) stratified by age based on the DREAM trial. The ERG notes that the DREAM trial was not powered to detect age-dependent utility reduction and that in the only age band that is affected by the implementation of age-adjusted utilities (65 years or more), there was only one single patient in DREAM. The ERG refers to the Technical Support Document (TSD) on the use of health state utility values in decision models,[5] where it is stated that "due to the increasing prevalence of comorbidities in older aged cohorts and the detrimental effect on HRQoL directly associated with age" utilities will not be constant and that adjusting for "the effects of age and gender should be conducted as an absolute minimum".

1.5 Age-adjusted mortality

The company undertook an analysis of asthma related mortality following hospitalisation stratified by age using a retrospective cohort study. It identified deaths that occurred during admissions to hospital with a specific asthma related ICD code of J46 (''acute severe asthma''; status asthmatics) within the same database as used by the Watson *et al.*[6] study (CHKS). The company then stratified the results by age using the same age stratification as Roberts *et al.*[7] The asthma related mortality rates following hospitalisation resulting from the company's study are shown in Table 5. A column with the rates

used by the ERG in its original base case (estimated combining Watson *et al.*[6] and Roberts *et al.*[7]) is provided for reference.

Table 5: Asthma related mortality rate following hospitalisation

Age	Deaths post admission	Admissions	Mortality rate	ERG's original base case*
0-11	9	13,348	0.0007	0.0015
12-16	5	2,844	0.0018	0.0014
17-44	52	17,601	0.0030	0.0020
45-54	45	4,875	0.0092	0.0076
55-64	48	3,152	0.0152	0.0214
≥65	188	4,136	0.0455	0.0454

*Estimated combining Watson *et al.*[6] and Roberts *et al.*[7]

The ERG welcomes the company's effort to address the shortcomings of the existing evidence regarding asthma related mortality after hospitalisation. The ERG is satisfied by the methods used in the observational study and acknowledges that the results of the study provide better estimates than those used in its original base case. However, the ERG notes that dividing the ≥65 into smaller age ranges such as 65-74, 74-85 and ≥85 would have provided a more accurate estimate of mortality rates as age increases. The ERG notes that if the mortality rate keeps increasing after 65 years, the company's assumptions would result in an ICER that was favourable to mepolizumab.

1.6 Continuation criteria

The original CC for mepolizumab was a non-worsening of the number of exacerbations from the previous year. Following the AC's conclusion that CC linked to improvement would have been more appropriate, the company proposed two variants of a composite alternative continuation criterion:

- a 50% (or 30%) reduction in the number of exacerbations compared with the previous year OR
- a reduction in mOCS dose while maintaining asthma control

The ERG believes that, with the available evidence, a robust ICER can only be calculated for the first criterion, the 30% or 50% reduction in the number of exacerbations, when there is no reduction in mOCS dose. The ERG also believes that the ICER relating to the second criterion (reduction in mOCS while maintaining asthma control) cannot be directly estimated using data from the MENSA trial as patients in MENSA were not allowed to reduce their mOCS dose. The ERG believes that an ICER should be calculated separately for those who have asthma exacerbation reduction and for those who reduce mOCS dose while maintaining asthma control: the ICER based on the composite continuation criterion should be calculated as the average of the ICER for patients who met the

criterion of exacerbation reduction and the ICER for patients who met the criterion of mOCS reduction while maintaining asthma control, weighted by the proportion of patients in each group.

The ERG shared its concern regarding this issue with the company during clarification. The company acknowledged that it is difficult to use the model to provide an estimate of the ICER for people who have a reduction in mOCS dose only. The company added that due to lack of evidence it was not possible to estimate a utility benefit of OCS dose reduction. The company implied that the ICER estimated based on the original continuation criterion (no worsening of exacerbations) could be used as an upper bound for the new continuation criteria. The ERG disagrees and argues that the ICERs based on exacerbation rates from MENSA and COSMOS will only be valid estimates for a setting where OCS dose is maintained. OCS reduction is likely to affect exacerbation rates, which are main drivers of the ICER.

1.7 Other aspects in the ACD

1.7.1 Age of eosinophilic asthma patients in the UK

The company argued against the AC's conclusion that the age assumed in the model was likely to be older than seen in clinical practice. It argued that the proposed population for mepolizumab featured an especially late onset and referred to two studies [8, 9] that reported mean ages at baseline of 49, 50 and 59 years depending on the source. However, the only reported mean age at onset of symptoms was 34.5.[8] The company also provided descriptive data on the age distribution of the MENSA trial and presented a scenario analysis using the median age in MENSA (52 years): the ERG believes that the mean is more appropriate. The ERG requested from the company via NICE the mean age of the accepted population, as it believed it was more appropriate to use the mean age of the accepted population than that of the ITT population. The company reported that the mean age of the accepted population was slightly higher (51.5 years) than that of the ITT population (50.1 years). The ERG notes that the company referred to two studies in their first response to the ACD,[10, 11] which reported mean ages of 44.9 and 45 years for severe and eosinophilic asthma. Furthermore, the ERG notes that, should mepolizumab be recommended, it is likely that the mean age of patients at start of treatment would be lower than the mean age of patients with severe eosinophilic asthma. Patients would start being treated with mepolizumab soon after the onset of severe eosinophilic asthma whereas it is likely that patients recruited to the MENSA trial would have been suffering from severe asthma for a number of years. The ERG undertook sensitivity analyses to assess the impact of this uncertainty on the ICER of mepolizumab compared with SoC.

1.7.2 Consideration of waning of treatment effect

The company argued that there is no clinical reason to expect a waning of the efficacy of mepolizumab and that none of the patients that developed antibodies in the trials suffered from a reduced efficacy. The company also claimed that there was no evidence of waning effect in omalizumab, as well as clinician experts' views and the exacerbation rates in COSMOS. The company concluded that since there was no evidence of a waning effect, it should not be considered as an ongoing uncertainty in the analyses. The ERG notes that whilst there is no evidence of a waning effect, the available evidence does not prove continuous long-term efficacy and therefore the uncertainty should still be considered.

1.7.3 Accounting for reduction in maintenance OCS use

In order to estimate the benefits of the reduction in mOCS dose, the company referred to TA278,[12] the appraisal of omalizumab, which modelled the costs and consequences of OCS use in patients with severe asthma. The company presented figures of the impact of incorporating mOCS adverse events on the ICER of omalizumab versus SoC reported in published articles,[13, 14] in the assessment report and the final appraisal determination (FAD). The impact on the different estimates of the ICER ranged from £4,000 to £17,000. Due to uncertainty around which ICER was used for decision-making in the omalizumab TA, the company decided to apply a reduction of £4,000-£9,000 to the ICER as a scenario analysis. The company acknowledges this is a crude estimate but argued that it helps quantify the impact of OCS sparing.

The ERG notes that applying a reduction of £4,000-£9,000 to the ICER of mepolizumab compared with SoC is not appropriate for the following reasons: the ICERs reported by the company from the omalizumab appraisal are specific to the mOCS subgroup and therefore cannot be applied to the accepted population for mepolizumab, which also includes a substantial proportion of patients that are not on mOCS; the impact on the ICER of omalizumab versus SoC is based on a 41.9% of patients on mOCS meeting the CC that discontinued mOCS whilst only 14.5% of patients in the SIRIUS trial discontinued mOCS; the mepolizumab efficacy estimates (exacerbation rates) used to calculate the ICERs in the accepted population of mepolizumab are based on the MENSA trial where OCS reduction was not permitted and therefore it is not appropriate to combine these exacerbation rates with benefits related to OCS reduction; and, due to the ICER being a ratio, it is not be appropriate to apply reductions in one ICER to another, as the same amount of incremental QALYs and costs will have a different impact on different ICERs.

The ERG acknowledges that there are benefits from the reduction of mOCS dose that have not been captured in the economic model, which would lower the ICER of mepolizumab compared with SoC. However, the ERG notes that a reduction in the dose of mOCS is also likely to lead to an increase in

the exacerbation rates used in the model, which would increase the ICER: it is unclear how these opposing effects would jointly affect the ICER.

1.8 Comparison with omalizumab

The company acknowledged the uncertainty around the comparative efficacy of mepolizumab versus omalizumab but asked the AC to reconsider the comparison with omalizumab in the light of the new PAS price. The company believes that for patients in the population eligible for either mepolizumab and omalizumab, clinicians should be able to prescribe the medicine that is most appropriate for the patients based on their phenotype.

The ERG agrees with the company that based on the available evidence, there is not enough evidence to recommend one treatment in preference of the other in the overlap population. The ERG acknowledges, however, that the cost of mepolizumab (annual cost of [redacted]) compared favourably with the cost of omalizumab based on the latter's list price (annual cost of £8,056). The ERG provided a similar cost analysis considering the confidential PAS price of omalizumab in a confidential appendix.

1.9 Calculation of the percentage of patients meeting the CC

The company changed the way in which it calculated the percentage of patients meeting the CC: instead of taking into account all the patients in MENSA (176), it considered only the patients from MENSA that continued on COSMOS (159). Hence, the percentages of patients meeting the newly proposed CC were calculated as the proportion of patients from MENSA that went on to COSMOS that met the CC. However, the percentage of patients meeting the original CC (157/176, 89.2%) was not updated, which led to an inconsistency. The company acknowledged the inconsistency in the clarification response[3] and presented an amended percentage (143/159, 89.9%). This change affected the analyses and the company presented amended results for their base case analysis. The results reported in this report are based on the amended percentage.

1.10 Attrition rates for the accepted population

The ERG notes that the annual treatment discontinuation or attrition rate used in the company's base case was assumed to be equal to the discontinuation rate in the ITT population during COSMOS. The ERG notes that this could be an underestimate given that patients are prone to discontinue treatment more in clinical practice than in a trial. However, the ERG noted during the clarification round that, in lack of a better estimate, it is more appropriate to use the discontinuation rate of patients in the accepted population. The company presented two discontinuation rates based on the patients of the accepted population who met the CC and moved into COSMOS: 11.5% (14/122) for the 50%

reduction in exacerbation rate CC and 11.9% (16/134) for the 30% reduction CC. The company did not provide the discontinuation rate for the original "no worsening" CC, therefore the ERG decided to assume it was equal to that of the 30% reduction CC in its analyses as a surrogate.

The ERG also considered the appropriateness of applying a constant attrition rate. The ERG believes that whilst it is likely that a proportion of patients would discontinue the treatment every year, it is also not implausible that some patients would return to treatment after discontinuing, especially if the symptoms of asthma return and their exacerbation rate worsens. As such, the percentage of patients on treatment at a given point in time may reach a steady state, or at least reduce the aggregate discontinuation rate considerably. The ERG notes that the economic analysis does not contemplate this possibility. It was not feasible for the ERG to conduct such an analysis due to time constraints but did assess the impact of the uncertainty around the attrition rate in its exploratory analyses. It is believed that assuming that the percentage of patients remaining on treatment was at a steady state would be favourable to mepolizumab compared with SoC.

2 Summary of the new analyses presented by the company

The company presented new analyses based on the ERG's amended model provided as part of the "ERG's critique to the company's response to the ACD", to which they applied the changes summarised in Table 6.

Table 6: Changes applied by the company to AC's preferred base case

Parameter/assumption	Type of change	AC's preferred assumption / old value	Company's assumption / new value
Duration of the disutility caused by exacerbation	Alternative assumption	Use MENSA mean durations of exacerbations	Use midpoint between Lloyd and MENSA
Treatment-dependent utilities	Alternative assumption	No utility gain obtained for mepolizumab treatment on top of exacerbation reduction	Different utilities based on DREAM for on and off treatment
Age-adjustment of utilities	Alternative assumption	Yes	No
Price of mepolizumab vial	New price	[redacted]	[redacted]
EQ-5D	New evidence	Unadjusted	Baseline adjusted
Asthma-related mortality	New evidence	Combination of Watson *et al.*[6] and Roberts *et al.*[7]	Results from company's new observational study

The company presented results for their base case analysis (Table 7) using the original continuation criterion and the proposed two alternatives: 50% reduction in the number of exacerbations; and 30% reduction in the number of exacerbations. The ICER for mepolizumab compared with SoC ranged from £27,418 per QALY gained with the 50% exacerbation reduction CC to £32,235 per QALY gained with the original CC. The company presented a scenario analysis where it applied a £4,000-£9,000 reduction to these ICERs as an estimate of the benefits of OCS sparing. The ERG argued against the validity of such an estimate in Section 1.7.3.

Table 7: Results of the company's base case analysis: mepolizumab vs. SoC

	Δ QALYs	Δ Costs (£)	ICER (£/QALY)
Original CC: no worsening of exacerbations*	[redacted]	[redacted]	32,235
Revised CC: 30% reduction	[redacted]	[redacted]	28,398
Revised CC: 50% reduction	[redacted]	[redacted]	27,418

*Based on the amended percentage of patients meeting CC, as explained in Section 0

The company also presented scenario analyses combining the following alternative assumptions:

- Using duration of exacerbations from MENSA instead of the midpoint between Lloyd *et al.*[1] and MENSA
- Using age-adjusted utilities
- Applying the EQ-5D mapped from SGRQ values
- Using the median age (52 years) instead of the mean age (50.1 years) of the trial population

The ICERs for mepolizumab compared with SoC ranged between £23,212 and £32,475 per QALY gained for the original CC (no worsening in exacerbation rate), between £23,193 and £29,828 based on the 30% reduction in exacerbations, and between £21,275 and £28,134 based on the 50% reduction in exacerbations.

3 Additional analyses undertaken by the ERG

The ERG undertook additional exploratory analyses to estimate the most likely ICER based on the AC's assumptions within ACD2 using the new PAS price and the new evidence supplied by the company both in its response to the ACD2 (mortality rates, baseline adjusted EQ-5D scores) and in its clarification response[3] (*i.e.* mean age and attrition rates of the accepted population). The ERG also performed the following scenario analyses to assess the impact on the ICER of each change to the

base case analysis used for the second AC meeting, including the new information provided by the company:

1. New asthma related mortality rates
2. Percentage of patients meeting CC based on patients who continued in COSMOS
3. Mean age of accepted population (51.5 years)
4. Attrition rate of patients in the accepted population that met the CC in MENSA and continued in COSMOS
5. Duration of disutility of exacerbations: Midpoint between MENSA and Lloyd et al.[1]
6. Treatment dependent EQ-5D (baseline adjusted)
7. Treatment dependent EQ-5D (not adjusted for baseline imbalance)

The results for the scenario analyses undertaken by the ERG based on the original CC are shown in Table 8. Results are provided based on the AC's preferred assumptions as expressed in ACD2, using the old PAS price and the newly proposed PAS price. The results obtained when using the new PAS and applying each change to the AC's preferred base case, in isolation, are also provided as are the results produced when different alternative scenarios are combined: AC's preferred base case including the new evidence (scenarios 1-4); AC's preferred base case including the new evidence but with alternative assumptions for duration of disutility of exacerbations and baseline adjusted EQ-5D utilities used in the model (scenarios 1-6); and scenarios 1-6 but with the utilities adjusted by the ERG as explained in Section 1.3. Table 9 and Table 10 show key results for the new CC of 30% and 50% reduction of exacerbation rate respectively.

Table 8: Results of ERG's analyses for the original CC (no worsening of the exacerbation rate)

		Total QALYs	**Δ QALYs**	**Total cost**	**Δ Costs**	**ICER (vs.)**
AC's preferred base case (old PAS price)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£59,859
AC's preferred base case (new PAS price)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenarios based on AC's preferred base case (new PAS price)						
1) New asthma related mortality rates	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£50,941
2) % meeting CC based on patients who continued in COSMOS (89.9%)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£48,956

3) Mean age of accepted population (51.5 years)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£44,304
4) Attrition rate of patients that met the CC in the accepted population (11.9%)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£49,124
5) Duration of disutility of exacerbations: Midpoint MENSA and Lloyd *et al.*[1]	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£46,206
6) Treatment dependent EQ-5D (baseline adjusted)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£32,670
7) Treatment dependent EQ-5D (not adjusted for baseline imbalance)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£40,704
AC's preferred base case (new PAS) and new evidence (scenarios 1-4)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£48,084
AC's preferred base case (new PAS), new evidence & alternative assumptions (scenarios 1-6)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£31,895
ERG's most plausible base case: - Scenarios 1-6 - ERG's utility adjustment	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£31,895

Table 9: Results of ERG's analyses for the revised CC: 30% exacerbation reduction

		Total QALYs	**Δ QALYs**	**Total cost**	**Δ Costs**	**ICER (vs.)**
AC's preferred base case (new PAS price)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AC's preferred base case (new PAS) and new evidence (scenarios 1-4)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£49,376
AC's preferred base case (new PAS), new evidence & alternative assumptions (scenarios 1-6)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£29,179
ERG's most plausible base case: - Scenarios 1-6 - ERG's utility adjustment	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£31,378

Table 10: Results of ERG's analyses for the revised CC: 50% exacerbation reduction

		Total QALYs	Δ QALYs	Total cost	Δ Costs	ICER (vs.)
AC's preferred base case (new PAS price)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AC's preferred base case (new PAS) and new evidence (scenarios 1-4)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£45,831
AC's preferred base case (new PAS), new evidence & alternative assumptions (scenarios 1-6)	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£28,082
ERG's most plausible base case: - Scenarios 1-6 - ERG's utility adjustment	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£29,163

The ERG stated in Section 1.6 that it was not appropriate to assume that the new continuation criterion proposed by the company, a reduction in mOCS dose while maintaining asthma control, would have the same ICERs as calculated in Tables 8-10. The ERG noted that the company had not presented the necessary evidence to calculate an ICER for the subgroup of patients that did not met the exacerbation reduction criterion but had reduced their mOCS dose. However, the ERG notes that an approximate threshold could be estimated assuming the following: not attributing a benefit for mepolizumab due to symptom relief (the AC's preferred assumption); that the exacerbation rate would not be affected by mepolizumab; and no cost offsets. In this crude analysis the EQ-5D utility increment due to mOCS dose reduction would have to be at least [redacted] in order for the ICER of mepolizumab compared with SoC to be under £20,000 per QALY gained and at least [redacted] to be under £30,000 per QALY. [redacted] Based on scenarios 1-6 and including the ERG's amended utility values, assuming the same exacerbation rate for mepolizumab as for SoC, results in an ICER of £60,825 per QALY gained (Table 11). These results imply that, ignoring cost offsets, in patients where mepolizumab does not result in an exacerbation reduction, the mOCS dose reduction would have to result in [redacted] extra QALYs [redacted] for the ICER of mepolizumab versus SoC to be under £30,000 per QALY gained and [redacted] extra QALYs for the ICER to be under £20,000 per QALY gained. The ERG notes that, as explained in Section 1.6, the ICER for a CC that includes exacerbation reduction or mOCS dose reduction should be calculated as the average of the ICERs for the two subgroups of patients that met each continuation criterion, weighted by the proportion of patients in each subgroup. The ERG notes that this could produce ICERs significantly higher than those estimated in this report

and in the company's submission, which are based on patients who met the different exacerbation reduction criteria.

Table 11: Results of scenario analysis assuming no exacerbation reduction from mepolizumab

		Total QALYs	Δ QALYs	Total cost	Δ Costs	ICER (vs.)
ERG's most plausible base case assuming no exacerbation reduction from mepolizumab	SoC	[redacted]		[redacted]		
	Mepo	[redacted]	[redacted]	[redacted]	[redacted]	£60,825

The ERG performed additional exploratory analyses concerning: the mean age of the patients receiving mepolizumab; the attrition or treatment discontinuation rate; and the effect of a hypothetical waning of the effectiveness of mepolizumab. The ERG present the results of these analyses for two different scenarios: the AC's preferred base case as described in ACD2 including new evidence (scenarios 1-4); and for scenarios 1 to 6 combined with the utilities proposed by the ERG in Table 4.

As explained in Section 1.7.1, the AC concluded that the age assumed in the model was likely to be older than seen in clinical practice and there is uncertainty around which would be the mean age at the start of treatment for mepolizumab. The ERG explored the impact of lower ages at treatment start on the ICER of mepolizumab versus SoC (Table 12).

Table 12: Results of the sensitivity analysis on the age at treatment start on the ICER of mepolizumab versus SoC

	AC's preferred base case + new evidence (scenarios 1-4)			ERG's most plausible base case		
Age	**40**	**45**	**51.5***	**40**	**45**	**51.5***
No worsening	£88,281	£59,271	£48,084	£44,298	£35,988	£31,895
30% reduction	£93,662	£61,271	£49,376	£42,750	£34,927	£31,378
50% reduction	£86,751	£56,965	£45,831	£39,761	£32,557	£29,163

*Base case

The ERG assumed the annual attrition rate to be constant and equal to that observed in the accepted population within the COSMOS study. However, as explained in Section 1.10, it is not clear that the attrition rate would be constant and patients that had discontinued treatment in the past could return to the treatment when the symptoms or the exacerbation rate worsened. The ERG explored the impact of assuming no discontinuation or a lower discontinuation rate on the ICER (Table 13).

Table 13: Results of the sensitivity analysis on attrition rate on the ICER of mepolizumab versus SoC

	AC's preferred base case + new evidence (scenarios 1-4)			ERG's most plausible base case		
Attrition rate (annual)	**0**	**0.05**	**Base case***	**0**	**0.05**	**Base case***
No worsening	£40,881	£43,743	£48,084	£30,335	£30,655	£31,895
30% reduction	£39,667	£43,327	£49,376	£29,475	£29,860	£31,378
50% reduction	£36,386	£40,035	£45,831	£26,952	£27,519	£29,163

*Base case assumed to be 0.119 for no worsening and 30% exacerbation reduction and 0.116 for 50% reduction

Finally, the ERG explored the impact of a hypothetical waning of the effectiveness of mepolizumab on the results of the analysis. As in its critique of the company's response to the first ACD, the ERG undertook a scenario analysis where it 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'. To clarify, in the beginning, the patients who meet the CC will 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. Table 14 shows the results of this sensitivity analysis.

Table 14: Results of the sensitivity analysis on waning effect on the ICER of mepolizumab versus SoC

	AC's preferred base case + new evidence (scenarios 1-4)				ERG's most plausible base case			
Treatment effect duration (years)	**10**	**20**	**30**	**No waning***	**10**	**20**	**30**	**No waning***
No worsening	84,811	69,497	61,651	48,084	44,582	39,995	37,419	31,895
30% reduction	95,343	74,133	64,767	49,376	46,784	39,817	37,081	31,378
50% reduction	92,068	70,381	61,042	45,831	43,429	37,392	34,744	29,163

*Base case

4 Conclusion

The company presented new evidence and a new PAS price for mepolizumab in response to the ACD2. It also presented the results of new analyses based on the new price, new evidence and some alternative assumptions to those favoured by AC, along with justification for doing so. Following the AC's conclusion that continuation criteria linked to improvement would have been more appropriate, the company proposed two composite alternative CC: patients would continue treatment if their exacerbation rate was reduced by a certain amount (30% or 50%) or if their mOCS dose was reduced while maintaining asthma control. The ERG noted that the exacerbation rates used in the model were based on the MENSA trial, in which mOCS reduction was not allowed. Therefore, the ICERs of mepolizumab versus SoC presented by the company were only reflective of a setting where mOCS dose reduction did not happen and thus, where only the exacerbation reduction criterion would apply.

The company presented the ICERs for mepolizumab compared with SoC for a base case using some alternative assumptions to those expressed by the AC: £32,235 per QALY gained using the no worsening of exacerbations CC, £28,398 per QALY gained using the CC of a 30% reduction in the number of exacerbations and £27,418 per QALY gained using the CC of a 50% reduction in the number of exacerbations.

The ERG presented results for two additional base cases: AC's preferred assumptions as expressed in ACD2 including the new evidence presented by the company; and, what the ERG considered as the most plausible base case given the available evidence, including some alternative assumptions and the new evidence provided by the company. The main difference between the two base cases is whether mepolizumab is believed to have benefits over and above exacerbation reduction or not. The ICERs for mepolizumab compared with SoC for the AC's preferred base case were: £48,084 per QALY gained using the no worsening of exacerbations CC, £49,376 per QALY gained using the CC of a 30% reduction in the number of exacerbations and £45,831 per QALY gained using the CC of a 50% reduction in the number of exacerbations. The ICERs for mepolizumab compared with SoC based on the ERG's most plausible base case were: £31,895 per QALY gained using the no worsening of exacerbations CC, £31,378 per QALY gained using the CC of a 30% reduction in the number of exacerbations and £29,163 per QALY gained using the CC of a 50% reduction in the number of exacerbations.

The ERG believes that in order to calculate an ICER for a CC that includes either exacerbation reduction or reduction of mOCS dose while maintaining asthma control, and ICER should be calculated for the subgroup of patients meeting each of the two criteria. The ICER for the combined CC would then be the average of the two ICERs weighted by the proportion of patients in each subgroup. The ERG notes that it did not have access to the necessary evidence to calculate the ICER

of the subgroup of patients who did not the exacerbation reduction criterion but whose mOCS dose was reduced while maintaining asthma control. However, the ERG notes that based on the exploratory analyses presented in this report, the combined ICER is likely to be considerably higher than those presented in this report based exclusively on the exacerbation reduction criteria.

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Mepolizumab for treating severe eosinophilic asthma: A Single Technology Appraisal
ERG's critique of the company's response to the ACD2 - Comment on factual inaccuracies reported by the company

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Description of inaccuracy	Description of proposed amendment	Justification for amendment	ERG's comment
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%.	As noted in ERG response to company response to ACD1: 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%.
Section 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 to with a "–" sign	The ERG believes it is correct to dispose of the negative sign in the figures because it is clear from the text that these refer to disutilities.
Section 3.45 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."	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. We recommend to remove this statement.	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	The statement highlighted by the company contains no factual inaccuracies: it is not stated that 41.9% percent is the proportion of ITT patients in EXALT who stop OCS; it is stated that it is the percentage of patients who responded; and, it is implicit that the refers to the percentage of patients on mOCS. The ERG agrees that these figures are not directly comparable because the percentage reported in SIRIUS is not from responders or patients

		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.	who met the CC. However, this difference is stated in the text. The ERG notes that it is not the scope of this appraisal to assess the robustness of the evidence of omalizumab's efficacy and that the AC of TA278 accepted the validity of the evidence of EXALT, which was used for the analyses.
Section 3.48: Analysis 3 states, "patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year, and a blood eosinophil count of 300 cells/microlitre or more per year".	Analysis 3 should state, "patients on maintenance oral corticosteroids and/or 4 or more exacerbations in the previous year, and a blood eosinophil count of 300 cells/microlitre or more in the previous year.	This re-wording just provides additional clarification on the proposed population.	The ERG agrees with correction proposed by the company.
Section 4.7: It states, "Having considered all the comments, the committee concluded that the population in analysis 3, that is, people with a blood eosinophil count of 300 cells/microlitre or more per year and at least one of the following..."	This sentence should be re-phrased to state, "Having considered all the comments, the committee concluded that the population in analysis 3, that is, people with a blood eosinophil count of 300 cells/microlitre or more in the previous year and at least one of the following..."	This re-wording just provides additional clarification on the proposed population.	The ERG agrees with correction proposed by the company.

Summary of appraisal, 4:10: "In addition, its guidance would not apply to asthma that has previously been treated with omalizumab because evidence for this position in the treatment pathway was not presented". This is contradictory to what is stated in the Section 4.11.	In Section 4:11, it states "The company also presented further data from the MENSA trial stratified by prior omalizumab use, which showed that there is no evidence of differential effectiveness in people previously treated with omalizumab. The committee concluded that mepolizumab is effective in people previously treated with omalizumab".	Our assumption is that the summary statement is incorrect and should be re-worded to that stated in 4.11.	The ERG agrees with correction proposed by the company.
Section 4.15: It states, "Also, the committee considered that a 10% attrition rate seemed to be arbitrary and did not constitute a formal continuation rule"	This sentence should be removed.	There are two reasons for this as the continuation rule and the attrition rate are two separate and distinct parts of the model: i) In year 1, a continuation rule, of no worsening in exacerbation rates was applied, to the subpopulation in MENSA, which found that 89.2%, met the rule, and 10.9% did not meet the rule (applying the initially proposed continuation rule). This is a specific review and would only take place at 12 months. ii) The 10% annual attrition rate is applied to the model from year 2 onwards. This figure is estimated based on the clinical trial programme for mepolizumab, specifically in the one year OLE study, COSMOS, where 10% of patients withdrew from treatment with mepolizumab (66/651). This assumption of attrition reflects that, consistent with good clinical practice, the ongoing need for treatment with mepolizumab will continue to be reviewed on the basis of risk benefit to the patients, as well as	The ERG does not agree that the full sentence should be removed. It is true that the 10% attrition rate was not claimed to be a continuation rule, but it is also true that it seems arbitrary to assume that the discontinuation rate for COSMOS would apply as a constant attrition rate. Therefore the ERG would propose the following amendment: "Also, the committee considered that using an attrition rate 10% based on the discontinuation rate in COSMOS seemed to be arbitrary"

		patient choice/non adherence. It is therefore not clear why the 10% attrition rate is regarded as arbitrary, and we suggest this statement be removed. . Thus it has never been suggested that the attrition rate would constitute a formal continuation rule, and so this sentence should be removed as it is factually inaccurate.	

The ERG agrees with the corrections to the tables in the ACD included in the company's response, most of which were already included in the "Company response to ACD1 with errata". The ERG also agrees with the two corrections proposed by the company to the "ERG's critique of the company's response to the ACD".