NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Benralizumab for treating severe eosinophilic asthma [ID1129]

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:
   - AstraZeneca
   - Asthma UK
   - GlaxoSmithKline UK Ltd
   - NHS England Specialised Respiratory Clinical Reference Group
   - Teva UK Limited

   **RCP endorse the ACD and have made no comment*

3. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Tim Harrison nominated by AstraZeneca

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

5. **ERG critique of company ACD response**

6. **Expert personal perspective declaration** from:
   - Ms Olivia Allen – patient expert, nominated by Asthma UK

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

Benralizumab for treating severe eosinophilic asthma

Single Technology Appraisal

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

Type of stakeholder:

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.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Commentator	GSK UK Ltd	*Identification of the relevant evidence to inform the Matching-Adjusted Indirect Comparison of benralizumab vs. mepolizumab* We do not believe that evidence from DREAM should have been included as part of the basecase evidence for mepolizumab for the matching-adjusted indirect treatment comparison (or if it was, it should have been included as well as MUSCA – see comment 3) • Not all patients in the DREAM study (Phase IIb) meet the criteria for severe eosinophilic asthma due to underlying differences in the study inclusion criteria between DREAM and MENSA. While this was accounted for, by excluding inappropriate patients, in the analyses GSK submitted to NICE as part of the appraisal of mepolizumab, it was not, in this matching-adjusted indirect comparison. • The licensed dose and administration for mepolizumab is 100mg 4-weekly sub-cutaneous (SC) injection which was not studied in DREAM. We acknowledge the bio-equivalence of 75 mg IV to 100 mg SC, however this is not reason enough for inclusion of DREAM data in the basecase matching-adjusted indirect comparison, given the differences in the study inclusion criteria's (and given exclusion of the MUSCA data). • We believe that inclusion of the 75 mg IV mepolizumab data from DREAM, into the matching-adjusted indirect comparison would potentially over-inflate the numerical advantage shown for benralizumab.	Comment noted. The committee noted the uncertainty in this comparison concluding that 'there remains uncertainty about the clinical effectiveness of benralizumab compared with mepolizumab and reslizumab because the method used for the comparison with mepolizumab is not considered robust' (ACD2 section 3.7)
2	Commentator	GSK UK Ltd	*Identification of the relevant evidence to inform the Matching-adjusted indirect comparison of benralizumab vs. mepolizumab* We believe that the MUSCA study, studying the licenced mepolizumab dose (100mg SC) and an appropriate severe eosinophilic asthma population, should have been included as relevant evidence for mepolizumab in the basecase matching-adjusted indirect comparison. By excluding it, the numerical advantage for benralizumab is improved as concluded by the Committee in the ACD. • MUSCA (Chupp et al., 2017), a Phase 3b, placebo controlled, double blind, parallel group, multicentre study, was designed to assess the effect of add-on mepolizumab on disease-specific health related quality of life. • The primary efficacy end point was the mean change from baseline in St. Georges Respiratory Questionnaire at week 24. Other end points (all measured at week 24) included mean change from baseline in Asthma Control Questionnaire (v5) and annual rate of clinically significant exacerbations. • Therefore, MUSCA measured outcomes of interest to the matching adjusted indirect comparison • Even though the primary end point of MUSCA was the change from baseline in the St. Georges	Comment noted. The committee was aware that the effectiveness results for the MAIC were dependant on the trials included in the comparison. The committee concluded that there remains uncertainty about the clinical effectiveness of benralizumab compared with mepolizumab and reslizumab because the method used for the

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			Respiratory Questionnaire at week 24, this does not mean the study was not powered to detect differences in efficacy as suggested by AZ. For example, in MENSA (Ortega et al., 2014), it was estimated that with 180 patients in each group, the study would have a power of 90% to detect a 40% decrease in the exacerbation rate. In MUSCA (Chupp et al., 2017), there were 277 on the placebo arm and 274 on the mepolizumab arm i.e. sufficient power to detect differences in efficacy. • More importantly, the recruited population to MUSCA most closely matches the populations recruited to the benralizumab trials, SIROCCO (Bleecker et al., 2016) and CALIMA (Fitzgerald et al., 2016). • For example, the number of exacerbations in the previous 12 months for the intent to treat population at baseline was reported as: o SIROCCO (Bleecker et al., 2016) ▪ n=1204, 2.9 (SD 1.69) o CALIMA (Fitzgerald et al., 2016) ▪ n=1091, 2.7 (SD 1.62) o MUSCA (Chupp et al., 2017 and https://www.gsk-clinicalstudyregister.com/files2/gsk-200862-clinical-study-report-redact.pdf) ▪ n=551, 2.8 (SD 1.75) o MENSA (Ortega et al., 2014) ▪ n=576, 3.6 (SD 2.6) o DREAM (Pavord et al., 2012) ▪ n=616, 3.6 (SD 3.0) • Although the study duration of MUSCA was relatively short (24 weeks), for outcomes of interest defined by ratios, such as exacerbation rate ratios, study duration becomes less relevant. Further, MENSA was not substantially longer at 32 weeks and therefore we do not believe the reason for excluding MUSCA from the basecase matching adjusted indirect comparison is suitably substantiated. Further, the long-term efficacy of mepolizumab have been demonstrated through extension studies.	comparison with mepolizumab is not considered robust (ACD2 section 3.7)
3	Commentator	GSK UK Ltd	*Identification of the relevant evidence to inform the indirect comparison of benralizumab vs. mepolizumab* There are other published data for mepolizumab excluded from the indirect comparison which would have supported better matching of benralizumab and mepolizumab and could have directed towards an alternative indirect comparison approach. • AZ stated that evidence pertaining to the efficacy of mepolizumab in the NICE recommended population was limited (baseline or historic >=300 eosinophils /µL and either >= 4 exacerbations in the previous 12 months or continuous OCS use for the past 6 months). • AZ stated they identified one abstract reporting a post-hoc analysis of the MENSA study in patients with >=300 eosinophils /µL and 3 exacerbations in the prior year which demonstrated increased efficacy relative to the overall MENSA population. • However, AZ chose not to include this in the indirect comparison stating the data for the sub-group were available for only one, of the two mepolizumab exacerbation trials, MENSA (and not DREAM). • We disagree that this is reason to exclude the abstract.	Comment noted. The committee was aware that the effectiveness results for the MAIC were dependant on the trials included in the comparison. The committee concluded that 'there remains uncertainty about the clinical effectiveness of benralizumab compared with mepolizumab and reslizumab because the method used for the

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			○ The abstract still presents relevant evidence to the decision problem and could have been included in a sensitivity analysis to the indirect comparison. ▪ The rate ratio of mepolizumab vs. placebo for exacerbations among patients with a history of >=3 exacerbations in the past year and eosinophils of >=300 cells/μL at baseline was 0.34 (95% CI 0.23, 0.51) (Yancey et al., 2017). This compares to a rate ratio of benralizumab vs. placebo of 0.45 (95% CI 0.34-0.60) for the same population reported in the meta-analysis of SIROCCO and CALIMA (Fitzgerald et al., 2018, Table 6). • There is also a published meta-analysis of the MENSA and DREAM mepolizumab studies (Ortega et al., 2016). We disagree with the ERG's conclusion that this secondary analysis was appropriately excluded by AZ. This meta-analysis included an analysis of the reduction in exacerbation rate stratified by baseline blood eosinophil count which could have made an indirect comparison through other methods possible. ○ The rate ratio of mepolizumab vs placebo for reduction in exacerbations among patients with baseline eosinophils of >=300 cells/μL was 0.41 (95% CI 0.33, 0.51) (Ortega et al., 2016, Table 2). Further this rate ratio included a less severe population; patients with < 1.5 Asthma Control Questionnaire score (which were excluded from SIROCCO and CALIMA) and >= 2 exacerbations in the last year. It is likely that this rate ratio would have improved further in favour of mepolizumab in the more severe AZ proposed asthma population. The rate ratio was also reported for MENSA (0.39 [95% CI 0.28, 0.55]) and DREAM (0.42 [95% CI 0.31, 0.56]) separately.	comparison with mepolizumab is not considered robust' (ACD2 section 3.7)
4	Commentator	GSK UK Ltd	*The method of matching on baseline characteristics (as part of the matching adjusted indirect comparison) may have biased the results numerically in favour of benralizumab* Asthma Control Questionnaire version 6 (ACQ-6) is clearly a treatment effect modifier for benralizumab and yet this was not selected for matching with the mepolizumab population. • Table 40 in the ERG Report presents a summary of the selection of variables for matching to inform the matching-adjusted indirect comparison and shows that ACQ-6 is clearly a treatment effect modifier. This is further supported by the meta-analysis looking at predictors of enhanced response with benralizumab (Fitzgerald et al., 2018, Figure 2). • Table 40 of the ERG report states that AZ did not select ACQ-6 for matching because different scale versions were used in the mepolizumab studies (ACQ-6 was used in DREAM and ACQ-5 was used in MENSA) • We believe that matching could still have been performed. ○ The use of different versions of the ACQ in the different clinical trials (ACQ-7 in the reslizumab trials, ACQ-6 in the benralizumab trials and ACQ-5 and ACQ-6 in the mepolizumab trials) is a limitation; however, a number of validation studies have been published, including by the developers of the instruments, showing that all ACQ versions have similar psychometric properties, that the results with either instrument is very similar in large studies, including for change, and conclude that the three versions can be used without loss of validity or change in interpretation.	Comment noted. See response above

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			○ In accordance with this point, the mean ACQ-6 score for the ITT at baseline from DREAM was 2.4 (SD 1.1) (Pavord et al.,2012) and the equivalent mean ACQ-5 score is 2.4 (SD 1.1) (Ortega et al., 2016). Compared with baseline mean ACQ-6 scores for SIROCCO 2.81 (SD 0.93) and CALIMA (2.76 SD 0.93) (FitzGerald et al., 2018) ○ We therefore believe it is possible to match on ACQ, a key treatment modifier and in doing so, this would have favoured mepolizumab.	
5	Commentator	GSK UK Ltd	*The method of matching on baseline characteristics (as part of the matching adjusted indirect comparison) may have biased the results numerically in favour of benralizumab* Matching of baseline eosinophil counts is based on two categories, ≥ 300 cells/μL and < 300 cells/μL. Clinically and methodologically, it would be appropriate to consider using more bands, especially given eosinophils is a very strong predictor of response. • Different clinicians define severe eosinophilic asthma by different eosinophil levels and these levels can vary based on clinical patient history. • Moreover, we know that increased baseline eosinophils results in increased response to mepolizumab and benralizumab. • For mepolizumab, the rate ratio for exacerbations, across a range of thresholds is reported (< 150 cells/μL, 150-<300 cells/μL, 300-<500 cells/μL and ≥ 500 cells/μL) which could have been matched with the benralizumab data. The resultant estimate for SIROCCO/CALIMA after adjustment may differed as a result of looking at different blood eosinophil categories.	Comment noted.
6	Commentator	GSK UK Ltd	*The method of matching on baseline characteristics (as part of the matching adjusted indirect comparison) may have biased the results numerically in favour of benralizumab* Matching on previous exacerbations in the last 12 months is based on two categories, 2 and >2. Clinically and methodologically, it might have been more appropriate to explore using a greater number of bands especially given clinician's views of patients with an increasing number of previous exacerbations. For example, a patient having experienced 3 exacerbations is different to another who may have experienced 5 exacerbations etc. For both mepolizumab and benralizumab studies, the proportion of patients with 2, 3, and >3 exacerbations in previous year was available. Matching based on these categories may have yielded very different results.	Comments noted
7	Commentator	GSK UK Ltd	*Interpretation of the matching adjusted indirect comparison results to more severe sub-groups* We disagree with the assumption that the relative treatment effects obtained from the matching adjusted indirect comparison can be carried forward to more severe patient subgroups. • AZ claims that they have not identified a reason why the relative treatment effect between benralizumab and mepolizumab would differ in the mepolizumab NICE-recommended population and that the relative treatment effect for benralizumab and mepolizumab as derived from the matching adjusted indirect comparison from the full trial populations can be applied to data for the mepolizumab NICE-recommended population. • There is published evidence to support why the relative treatment effect of benralizumab cannot be	Comment noted. The committee did not consider the rationale for conducting a MAIC to be consistent with applying the same relative difference in efficacy from the ITT to more severe patients

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			assumed to apply to more severe sub-populations. ○ The published meta-analysis of MENSA and DREAM (Ortega et al., 2016) clearly shows there is a dose response for add-on mepolizumab with increasing eosinophils at baseline. The reported rate ratio of mepolizumab vs. placebo for baseline eosinophils (EOS) is as follows: ▪ ≥ EOS 150 cells/μL is 0.48 (95% CI 0.39-0.58) ▪ ≥ EOS 300 cells/μL is 0.41 (95% CI 0.33-0.51) ▪ ≥ EOS 400 cells/μL is 0.34 (95% CI 0.27-0.44) ▪ ≥ EOS 500 cells/μL is 0.30 (95% CI 0.23-0.40). ○ The strength of this finding for mepolizumab is in contrast to that reported in the meta-analysis of the benralizumab studies (Fitzgerald et al., 2018). The reported rate ratio of benralizumab vs. placebo for baseline EOS is as follows: ▪ ≥ EOS 150 cells/μL is 0.63 (95% CI 0.53-0.74) ▪ ≥ EOS 300 cells/μL is 0.57 (95% CI 0.47-0.69) ▪ ≥ EOS 450 cells/μL is 0.50 (95% CI 0.38-0.64) ○ Published treatment effects estimate for mepolizumab (Ortega et al. 2016) and benralizumab (Fitzgerald et al., 2017) are presented below. With increasing eosinophils thresholds, there appears to be a trend towards further separation between mepolizumab and benralizumab in favour of mepolizumab. Although it needs to be interpreted with care, this comparison illustrates that the relative effects between the two treatments observed overall may not be carried forward across different sub-populations. This suggests that an indirect comparison based on subgroup analyses, such as that presented in Yancey et al., 2017 (which showed that the rate ratio of mepolizumab vs. placebo for exacerbations among patients with a history of >=3 exacerbations in the past year and eosinophils of >=300 cells/μL at baseline was 0.34 [95% CI 0.23, 0.51]) in the relevant sub-population for decision-making may be more appropriate than a matching adjusted indirect comparison in a wider population.	

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			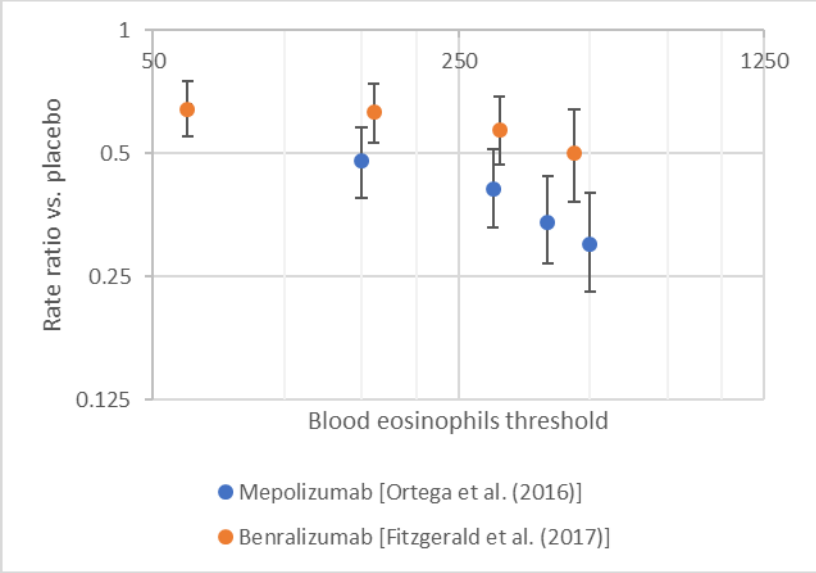 ○ Differences in effect modification seen by baseline eosinophils threshold may also exist by ACQ score or exacerbation history. However, there is currently insufficient information published to assess this. • On this basis, the underlying eosinophil treatment effect modifier may act to different extents for mepolizumab and benralizumab and therefore a matching-adjusted indirect comparison may no longer be a suitable method for an indirect comparison unless information on baseline characteristics within targeted populations are available. In the absence of this, a traditional indirect treatment comparison, such as using the Bucher method, may be more appropriate for comparing the efficacy of mepolizumab and benralizumab.	
8	Commentator	GSK UK Ltd	We agree with AZ's and ERG's conclusion that the matching adjusted indirect comparison attempted for benralizumab and mepolizumab populations on maintenance OCS (ZONDA and SIRIUS) must be interpreted with caution because of the differences in the study population, design and assessment of outcomes.	Comment noted
9	Commentator	GSK UK Ltd	Additional comments	
10	Commentator	GSK UK Ltd	The committee noted that benralizumab's convenience of administration is considered a 'step change' due to the 8-weekly dosing and therefore the need for patients to attend hospital less often for injections. We believe this is a short-term advantage. GSK would urge the committee to consider the transition of benralizumab and mepolizumab to patient self-administration over the next 12-18 months, [redacted] Taking learnings from other therapy areas where biologics given at home has become standard practice (e.g.	Comment noted. The ACD notes that the method of administration was a 'step change' for patients but there were not convinced that there

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			Rheumatoid Arthritis), respiratory medicine is looking ahead to formats soon to be made available (NICE has recently confirmed that mepolizumab in auto-injector form will be reviewed through the Commissioning Support Programme). [redacted]	were additional benefits that were not included in the QALY
11	Commentator	[Teva UK Limited]	We are concerned that the following statement in the ACD is not accurate: *'**reslizumab is not frequently used in clinical practice because it is given intravenously, which is not convenient for patients.'*** Reslizumab received its approval from NICE (TA479) nine (9) months later than mepolizumab. Usage of reslizumab is currently lower than mepolizumab as it was only recently funded by NHSE, but is already in routine use by several of the Tertiary Asthma centres in England. We also disagree that reslizumab is not convenient for patients. Currently both anti-IL5 biologics are administered monthly only within a hospital setting and therefore patients have to travel each month irrespective of the treatment given although we do accept that the route of administration is different.	Comment noted. The committee were aware that reslizumab guidance was in the process of being implemented which may explain lower uptake than expected. The committee heard from the patient and clinical experts that some patients although eligible for reslizumab or mepolizumab may choose not to take it for personal reasons.
12	Commentator	[Teva UK Limited]	We disagree with the following statement: ***'However, the clinical experts noted that the intravenous injections are a disadvantage and limit its use. The committee concluded that for people who have had 3 exacerbations and are not taking oral corticosteroids, the most appropriate comparator in current NHS practice is standard care.'*** Reslizumab does not have limited used according to its route of administration and post NICE approval (TA479) and NHSE funding is being used routinely by numerous tertiary asthma centres and is therefore included in current NHS practise and should be an appropriate comparator.	Comment noted. The committee heard from the patient and clinical experts that some patients although eligible for reslizumab or mepolizumab may choose not to take it for personal reasons.
13	Commentator	[Teva UK Limited]	We are concerned that with the following statement: ***'the company assumed that benralizumab and reslizumab have the same clinical efficacy.*** We agree with the following ERG statement: ***The ERG agreed that a MAIC comparing benralizumab with reslizumab is not feasible, but it noted that there is no evidence to support the assumption of clinical equivalence.'*** In addition we would like to draw to the committees attention a subgroup analysis from the reslizumab Phase III trial for patients with 3 or more CAEs that was presented at the European Respiratory Society (ERS) meeting last year which showed a difference compared to the subgroup analysis for benralizumab as quoted in the ACD for a	Comment noted. The committee considered the assumption of equivalence to be unproven. However, when it considered the impact of the difference in clinical efficacy on the ICER it noted that the ICERs were robust to this assumption and was therefore cost effective

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			similar patient population: Reslizumab: **67% (RR 0.33, 95% [0.22, 0.49])** published at the ERS 2017 Chauhan *et al.* compared to: Benralizumab **53% (RR 0.47, 95% [0.32 to 0.67])** as stated in the ACD	compared with reslizumab.
14	Commentator	[Teva UK Limited]	We are concerned that the following statement in the ACD is not accurate: ***'However, the committee noted that reslizumab is used much less frequently than mepolizumab in the NHS, and it considered that the comparison of benralizumab with reslizumab is not critical to its decision making.'*** Reslizumab only received its approval from NICE (TA479) in October which was nine (9) months later than mepolizumab. Usage of reslizumab will be lower than mepolizumab due to the later approval and was only recently funded by NHSE. Reslizumab is however already in routine use and therefore is critical to the decision making of the committee.	Comment noted. On consideration of the consultation comments the committee considered mepolizumab, reslizumab and standard care to be relevant comparators in different populations. The committee considered separately the clinical and cost effectiveness of benralizumab in people who were eligible for mepolizumab, both mepolizumab or reslizumab, reslizumab and standard care.
15	Professional Group	NHS England Specialised Respiratory Clinical Reference Group	NHS England note the input from the clinical experts regarding standard of care (SOC) for people who have had 3 or more exacerbations in the last year and view that statement as inaccurate. The Respiratory CRG clinical view is that reslizumab is now the SOC following the NICE HTA and at many severe asthma centres approximately 10-20% of anti-eosinophilic biologic prescribing is currently for reslizumab.	Comment noted. The committee were aware that reslizumab guidance was in the process of being implemented which may explain lower uptake than expected. The committee considered reslizumab to be a relevant comparator in some patients.

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16	Professional Group	NHS England Specialised Respiratory Clinical Reference Group	With regards to the statement from the clinical experts that 60% of people starting mepolizumab will be taking maintenance oral corticosteroids (OCS) the Respiratory CRG clinical view is that in their experience approximately 80% of people starting mepolizumab are on OCS. As this has a significant impact on the economic modelling NHS England would suggest obtaining the correct data. The UK severe asthma registry collects information on patients starting biologics and would be happy to provide this information.	Comment noted. The committee heard from the clinical expert that between 66 and 80% people starting on mepolizumab are taking OCS (ACD 2 section 3.9). The committee were aware that the uptake of newer biologic treatments is currently ongoing and the there was considerable uncertainty that the assumption that the proportion of people on OCS in the pivotal trial (and model) would be generalisable to clinical practice in England. These assumptions had a large impact on the calculated ICERs.
17	Professional Group	NHS England Specialised Respiratory Clinical Reference Group	Benralizumab is included in the 2018 iteration of Global Initiative for Asthma (GINA)	Comment noted
18	Professional Group	NHS England Specialised Respiratory Clinical Reference Group	The Respiratory CRG clinical view is that there is no evidence to suggest that reslizumab is OCS sparing, which is suggested on page 3.	Comment noted
19	Professional Group	NHS England Specialised Respiratory Clinical Reference Group	NHS England do support the development of products which can be self-administered as there is a significant burden on patients currently having to attend hospital services but would want to see this at a cost-effective price for the NHS.	Comment noted

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20	Professional Group	NHS England Specialised Respiratory Clinical Reference Group	NHS England note that NICE's assessment seems appropriate as the outcomes are the same as Mepolizumab and has no cost benefit.	Comment noted
21	Professional Group	NHS England Specialised Respiratory Clinical Reference Group	The Respiratory CRG Patient and Public Voice member (Asthma UK) will be submitting their own organisational response.	Comment noted
22	Patient Group	Asthma UK	**Response on behalf of Asthma UK** Asthma is one of the most prevalent long-term conditions in the UK, with 5.4 million people currently receiving treatment. Severe asthma affects nearly 5% of people with asthma – around 250,000 people in the UK, of whom a subgroup of around 40% will have an eosinophilic phenotype. The National Review of Asthma Deaths highlighted that almost 40% of those who died had severe asthma[1]. Though existing biologics have offered relief of symptoms to some, they are limited in that they are only made available to a specific sub-population. As such, the approval of a new biologic offers an opportunity to help more people with severe asthma.	Comment noted
23	Patient Group	Asthma UK	**Consequences of the current decision not to approve Benralizumab** A. Impact on the lives of people with severe asthma: • There are only limited treatment options available to people with severe eosinophilic asthma. • Oral corticosteroids are not very effective at controlling severe asthma and they can have toxic and debilitating side-effects	Comments noted. The committee considered separately the clinical and cost effectiveness of benralizumab in people who were eligible for mepolizumab, both mepolizumab or reslizumab, reslizumab and standard care. Benralizumab has now

[1] M. Levy et al., 'Why Asthma Still Kills: The National Review of Asthma Deaths (NRAD)', Report or Working Paper, 6 May 2014, https://www.rcplondon.ac.uk/projects/national-review-asthma-deaths.

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			• Despite adhering to current recommended asthma treatments, symptoms can persist and patients' asthma can remain uncontrolled, putting them at risk of potentially life-threatening attacks as well as significantly disrupting their quality of life. • Benralizumab could provide an (additional) alternative option for people with severe eosinophilic asthma who respond poorly to oral steroids. B. Cost to the health care system: • People with uncontrolled severe asthma cost four times as much as the average patient[2]. • Approving an additional biologic to help with the management of severe asthma will reduce the number of exacerbations and A&E visits or hospital admissions	been recommended in patients who are eligible for reslizumab if mepolizumab is not a treatment option.
24	Professional Group	Royal College of Physicians	The RCP is grateful for the opportunity to respond to the above consultation. We are happy with the ACD and are in full agreement.	Comment noted
25	Clinical expert	University of Nottingham	1. I believe the estimate for maintenance oral steroid use of 47% is too low. This figure is based on data from the BTS severe asthma register which includes all patients with severe asthma many of whom are less severe than the pool being considered for biological treatment. As discussed at the first meeting we have seen 66% of patients being considered for mepolizumab to be on maintenance prednisolone and discussions with other severe asthma centres suggests this to be a better estimate. 2. Although Meopolizumab is the main comparator for patients on maintenance prednisolone or 4 plus exacerbations, standard care is also appropriate for patients who prefer not to travel for many hours to receive a 4-weekly injection. These patients choose therefore to remain on standard care and this should be used as the comparator for these patients. 3. I can see no problem with having 4 plus exacerbations for one drug and 3 plus for another drug, we already have this for Resilizumab and it seems unlikely that all future biologics will fit under the same criteria in the hope of 'keeping it simple'.	Comment noted. The committee were aware

[2] Marjan Kerkhof et al., 'Healthcare Resource Use and Costs of Severe, Uncontrolled Eosinophilic Asthma in the UK General Population', *Thorax*, 16 September 2017, thoraxjnl-2017-210531, https://doi.org/10.1136/thoraxjnl-2017-210531.

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26	Clinical expert	Scottish Centre for Respiratory Research Ninewells Hospital University of Dundee	I wish to express my concerns about the recent NICE benralizumab appraisal document [ID1129] which I read today From what I can see NICE have compared benralizumab to mepolizumab on top of standard of care (SOC) as ICS/LABA in severe eosinophilic asthma (SEA) patients who have 4 or more exacerbations in previous year. In my clinical experience I would say approximately 5-10% of my patients with these criteria are actually receiving mepolizumab -ie SOC in most of my severe eosinophilic asthma patients in fact does not include Mepolizimab per se -which is therefore not SOC in the majority of patients . I would also say that the data in terms of clinical benefit are very compelling for adding benralizumab on top of SOC (as ICS/LABA) in SEA patients who have 3 or more exacerbations. Hence in my humble opinion it this is group of patients which should be used for the cost effectiveness analysis by NICE.	Comment noted. The committee were aware that the uptake of mepolizumab and reslizumab is lower than expected because the guidance is still in the process of being implemented. The committee considered separately the clinical and cost effectiveness of benralizumab in people who were eligible for mepolizumab, both mepolizumab or reslizumab, reslizumab and standard care. Furthermore, the committee was particularly interested in the cost effectiveness of benralizumab compared with SoC in those not eligible for other biologics. Although the company presented no specific ICER for that group, the evidence indicated that the ICER would full outside the cost effective range
27	Company	AstraZeneca	**1.Revised Patient Access Scheme (PAS)** In response to the ACD, AstraZeneca has revised the PAS, such that the price of benralizumab is reduced to [redacted] per vial (previously [redacted]).	Comment noted
28	Company	AstraZeneca	**2. With a revised Patient Access Scheme, benralizumab is cost-effective versus SOC in the population where a recommendation is sought** Including a revised Patient Access Scheme and updated economic model inputs (aligned with the discussion at the committee meeting), we present new analysis showing that benralizumab is a cost-effective option for patients with severe asthma with 300+ eosinophils, AND either 3+ exacerbations in	Comment noted. The committee did not consider the mixed population proposed by the company to be suitable for decision

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			prior year OR receiving maintenance OCS (base-case population). The ICER in the base-case population versus standard of care is £29,896.	making because of the mix of severity of eosinophilic asthma within the mixed population, its lack of generalisability to patients in England and differences in the cost effectiveness of benralizumab depending on the severity of asthma.
29	Company	AstraZeneca	**3. The most relevant comparators are both mepolizumab and SOC** We agree with the committee that the most relevant comparators in this appraisal are both mepolizumab and standard of care; however, we do not agree that in the mepolizumab NICE-recommended population (300+ EOS; AND either 4+ exacerbations in prior year OR receiving maintenance OCS) that the only relevant comparator is mepolizumab as we believe that high dose ICS/LABA (standard of care) is still established NHS practice in England, and therefore both mepolizumab and standard of care are relevant comparators in this population. We present an analysis of prescription data, which demonstrates that of those patients eligible for treatment with mepolizumab, only a minority are actually receiving mepolizumab. This shows that standard of care is still established NHS practice in England. The ACD for benralizumab for the treatment of severe asthma states "Mepolizumab is the relevant comparator for people who have had at least 4 exacerbations or are taking maintenance oral corticosteroids" The NICE methods guide section 6.2.2 states that when selecting the most appropriate comparator(s), the Committee will consider: • established NHS practice in England • the natural history of the condition without suitable treatment • existing NICE guidance • cost effectiveness • the licensing status of the comparator Further, section 6.2.3 states "The Committee will normally be guided by established practice in the NHS when identifying the appropriate comparator(s)" Given that mepolizumab gained a NICE recommendation recently (in 2017), the majority of patients eligible for mepolizumab are still receiving standard of care; thus, mepolizumab should not be considered to be the only established NHS practice for the treatment of these patients. Therefore, both standard of care and mepolizumab should be considered as comparators for these patients.	Comment noted. The committee considered separately the clinical and cost effectiveness of benralizumab in people who were eligible for mepolizumab, both mepolizumab or reslizumab, reslizumab and standard care. Benralizumab has now been recommended in patients who are eligible for reslizumab if mepolizumab is not a treatment option

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			In order to corroborate this, AstraZeneca has undertaken an analysis of IQVIA prescriptions data to better understand the level of uptake of mepolizumab. If we assume that one patient equates to one pack of mepolizumab for any given month then, as of March 2018, 1,677 (IQVIA, 2018) patients in the UK are currently receiving treatment with mepolizumab. The budget impact section of the manufacturer's submission for the NICE appraisal of mepolizumab estimates the number of eligible patients for mepolizumab to be 16,361* in 2018. Based on this, only 10.2% of eligible patients are being treated with mepolizumab and the remaining 89.8% are being treated with SoC (we recognise that a minority of these patients may also be receiving treatment with omalizumab or reslizumab). It should be noted that this population reflects the one originally submitted in the manufacturer's submission (≥150 eosinophils) rather than that within the final recommendation (≥300 eosinophils). If we revise this eligible population estimate through reducing the eligible population by an assumed one-third, to take account of this change in the eosinophil cut off, then this still shows that only 15.5% of eligible patients are being treated with mepolizumab (the remaining 84.5% being treated with SoC). AstraZeneca approached 14 severe asthma centre lead consultants to ask for their views on the ACD including their views on this topic. Five of these consultants did not share their views with AstraZeneca (3 had a conflict of interest; 2 were on holiday). Of the 9 who shared their views, 8 consultants stated that the most relevant comparators for the mepolizumab-eligible population are both mepolizumab and SOC**. For these reasons, we continue to present cost-effectiveness analysis vs. SoC in the base case population (300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS, and vs mepolizumab in the mepolizumab NICE-recommended population); we do not present cost-effectiveness analysis for benralizumab vs. SoC in patients with (exactly) 3 exacerbations in the prior year, who are not taking oral corticosteroids, a population eluded to in the ACD.	
30	Company	AstraZeneca	**4. Matching-adjusted indirect comparison (MAIC) is the most appropriate method to estimate relative efficacy of benralizumab versus mepolizumab** Rationale: In the absence of head to head trial data, this method adjusts for differences between the benralizumab and mepolizumab trials to provide a more accurate estimate of relative efficacy to inform decision-making, which is not possible in a network meta-analysis (NMA). [redacted] Based on the data provided below and patient benefits described above, we ask the Committee to recommend benralizumab in the specified population (300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS), to ensure that clinicians and patients have access to a treatment with specific patient benefits where there is high unmet need.	Comment noted. The committee considered that despite the rationale provided during consultation, the use of the MAIC instead of an NMA had not been adequately justified. The committee concluded that there remains uncertainty about the clinical effectiveness of benralizumab compared with mepolizumab and reslizumab because the method used for the

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
From the Committee meeting and the subsequent ACD, we understand the Committee's viewpoint that there is significant uncertainty associated with the relative treatment effects of benralizumab versus mepolizumab. However, we maintain that MAIC is the most appropriate approach to compare the relative treatment effect of benralizumab with mepolizumab in the absence of head-to-head studies and in line with NICE Decision Support Unit technical support document no. 18 (Phillippo 2016). A summary of the comparative advantages and limitations of NMA and MAIC to compare benralizumab with mepolizumab is presented in the table below.
Table 1: Key advantages and limitations of standard NMA and MAIC to assess the relative efficacy of benralizumab versus mepolizumab
<table>
<tr><th>Approach</th><th>Advantages</th><th>Limitations</th></tr>
<tr><td>MAIC</td><td>• Adjusts for differences between the benralizumab and mepolizumab trials by reweighting patients to provide a more accurate estimate of relative efficacy to inform decision-making (which is not possible in an NMA)
• Uses individual patient data (IPD) for benralizumab and aggregate data for mepolizumab to use the largest data-set possible with the data available to AZ</td><td>• Differences in eligibility criteria for OCS or discontinuation between the OCS-sp could not be adjusted for using MAIC (t also be the case in an NMA)</td></tr>
<tr><td>Standard NMA</td><td>• Enables a comparison of all three medicines (benralizumab, mepolizumab, and reslizumab), although limited by high heterogeneity so the results should not inform decision-making</td><td>• Differences between benralizumab and mepolizumab trials are not adjusted for, the principle of exchangeability required NMA does not hold, and making it an inappropriate method
• Very high level of heterogeneity meaning results from the NMA would not provide estimate of relative effectiveness betwee medicines, and could misinform decision
• Would use aggregate data for both ben</td></tr>
</table>
</td><td>comparison with mepolizumab is not considered robust and a simple assumption of equivalence, with no underpinning evidence was used for reslizumab (ACD2 section 3.7)</td></tr>
</table>

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			and mepolizumab, so would not capitalise on IPD available to AstraZeneca for benralizumab	

IPD: individual patient data; MAIC: matching-adjusted indirect comparison; NMA: network meta-analysis

If an NMA were to be conducted, there would be a very high level of heterogeneity that would be ignored in the analysis, meaning that results from the NMA would not provide a robust estimate of relative effectiveness between the three medicines, and could misinform decision-making. This is because the principle of exchangeability does not hold due to substantial differences between the benralizumab and mepolizumab trials.

The MAIC method adjusts for the differences between the benralizumab and mepolizumab trials, to give an estimate of relative efficacy that incorporates this known uncertainty, and so is a more appropriate guide to inform decision-making. We recognise that MAIC is associated with limitations such as the potential for the occurrence of extreme weights, but believe that these limitations are considerably outweighed by the advantage of adjusting for cross-trial differences.

In the MAIC analysis, [redacted]

The MAIC was conducted using ITT data from the trials, as the literature searches found no data for mepolizumab in the subgroup where it is NICE-recommended. We assumed that the relative treatment effect for benralizumab versus mepolizumab as derived from the MAIC in the full trial populations is generalisable to the mepolizumab NICE-recommended population. The relative difference between treatments was applied to the benralizumab data for the mepolizumab NICE-recommended population (300+ EOS; AND either 4+ exacerbations in prior year OR receiving maintenance OCS) to inform the economic model. Although this assumption is unverified, we have not identified a reason why the relative effect between benralizumab and mepolizumab would differ in the mepolizumab NICE-recommended population, or a better way to compare the two treatments.

In summary, we believe that MAIC is the most appropriate methodology to compare the relative effect

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			of benralizumab and mepolizumab, given the limited data available at this time. A more detailed description of the features and relative merits of NMA and MAIC is presented in Appendix 2, along with further details on how the MAIC results have been applied in the model. In-depth results of the MAIC are presented in Appendix 3. [redacted]	
31	Company	AstraZeneca	5.Model Inputs In this section, we outline the assumptions that have been employed in the revised cost-effectiveness analysis. Revised Patient Access Scheme (PAS) In response to the ACD, AstraZeneca has revised the PAS, such that the price per vial of benralizumab is reduced to [redacted] per vial (previously [redacted]). Mortality Whilst we agree with the ERG that asthma-related mortality has decreased in the UK since 2007 when Watson et al was published, we are concerned that data on mortality from a patient cohort of all asthma severities may not be the most appropriate to apply to a severe asthma population. However, in the absence of any recent data specific to this population, we have included the ERG's scaling of mortality risk in the economic model, but we consider this to be a conservative assumption. Percentage of patients on mOCS at baseline The ERG base case includes a figure of 41.7% of patients being on mOCS at baseline, for both populations, which is sourced from Heaney et al. However, during the discussion at the committee meeting it was clear that this figure, based on a population of all severe asthmatics (i.e. not taking into account eosinophils or exacerbation history) would be an underestimate. We believe that our original figure of 54.1%, which is based on a robust, sub-analysis of UK RWE data is the most appropriate to use in the base case population (300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS). This is further validated as the clinical experts at the meeting suggested that a figure of 60% would be	Comment noted. The committee noted that many of the model inputs in the revised model were consistent with the ERG/committee preferred assumptions and that the PAS had been updated. The committee noted that it is difficult to determine the proportion of people taking maintenance oral corticosteroids in the company's mixed population (ACD2 section 3.6). This is a key area of uncertainty in the model, which has a substantial impact on the cost effectiveness of benralizumab.

<table>
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<tr><td></td><td></td><td></td><td>
more appropriate for the mepolizumab NICE-recommended population. It follows from this that if 41.7% of all severe asthmatic patients are on mOCS, and 60% of those patients who meet the criteria for the mepolizumab NICE-recommended population are on mOCS, then the percentage of patients who are on mOCS in the base case population (300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS) must lie between these two figures.

As previously mentioned, the clinical experts at the meeting suggested that a figure of 60%, which is lower than the 78% from the robust UK RWE in the relevant patient population, would be more appropriate for the mepolizumab NICE-recommended population. To provide a conservative estimate of cost effectiveness, we have included the 60% figure in our revised analyses, although we believe this may be an underestimate.

<u>Administration time</u>

During the discussion at the committee meeting, the subject of administration time for benralizumab and mepolizumab was raised. The ERG had made the assumption in their base case that it would take the same amount of time to administer both mepolizumab and benralizumab; however, the clinical experts stated that it would be more appropriate to assume that mepolizumab took 15 minutes longer than benralizumab to administer, due to the need to reconstitute mepolizumab prior to administration.

We have therefore assumed a 15-minute administration time saving for benralizumab versus mepolizumab in our revised base case.

<u>Summary of model inputs</u>

Table 2: Summary of economic model inputs
<table>
<tr><td>Input</td><td>Value</td><td>Justification</td></tr>
<tr><td>Price of benralizumab</td><td>[redacted] per vial</td><td>Revised PAS</td></tr>
<tr><td>Mortality associated to Asthma exacerbations</td><td>Scaled by 0.4</td><td>As per ERG base case</td></tr>
<tr><td>% patients on mOCS</td><td>54.1% in the base case population</td><td>As per UK RWE</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>60% in the mepolizumab NICE recommended population</td><td>As per committee meeting clinical expert opinion and ACD document</td></tr>
<tr><td>Administration time</td><td>5 minutes for benralizumab

20 minutes for mepolizumab</td><td>As per committee meeting clinical expert opinion</td></tr>
<tr><td>Clinical effectiveness of benralizumab vs mepolizumab</td><td>As per MAIC results</td><td>MAIC is the most appropriate way of assessing relative clinical effectiveness between these two medications (see section 2)</td></tr>
<tr><td>Treatment discontinuation</td><td>Set at 0.0041 per cycle</td><td>As per ERG base case</td></tr>
<tr><td colspan="3">All other model inputs remain as in manufacturer submission base case</td></tr>
</table>
</td><td></td></tr>
<tr><td>32</td><td>Company</td><td>AstraZeneca</td><td>
<u>6. Cost-effectiveness results</u>

Incorporating the modelling assumptions mentioned above results in an ICER versus standard of care in the base case population (300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS) of £29,896, as shown in Table 3 below.

Table 3: Cost effectiveness results vs SoC in Base Case population
<table>
<tr><th>Scenario</th><th></th><th>Total cost</th><th>Δ cost</th><th>Total QALYs</th><th>Δ QALYs</th><th></th></tr>
<tr><td rowspan="2">Base Case</td><td>Benralizumab</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td></td></tr>
<tr><td>SoC</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td><td></td></tr>
</table>
</td><td>Comment noted. The committee considered the updated cost effectiveness analysis provided by the company and the ERG's confidential analysis which incorporated the PAS price for all biological agents. The committee did not consider the mixed population proposed by the company to be appropriate for decision making. The committee considered separately the clinical and cost</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>Table 4 below shows the revised cost effectiveness analysis vs mepolizumab in the mepolizumab NICE recommended population (300+ EOS; AND either 4+ exacerbations in prior year OR receiving maintenance OCS).

Table 4: Cost effectiveness results vs mepolizumab in mepolizumab NICE reccommended population*
<table>
<tr><th>Scenario</th><th></th><th>Total cost</th><th>Δ cost</th><th>Total QALYs</th><th>Δ QALYs</th><th></th></tr>
<tr><td rowspan="2">Base Case</td><td>Benralizumab</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>D</td></tr>
<tr><td>Mepolizumab</td><td>[redacted]</td><td></td><td>[redacted]</td><td></td><td></td></tr>
</table>
*Benralizumab net price vs mepolizumab list price</td><td>effectiveness of benralizumab in people who were eligible for mepolizumab, both mepolizumab or reslizumab, reslizumab and standard care. Benralizumab has now been recommended in patients who are eligible for reslizumab if mepolizumab is not a treatment option</td></tr>
</table>

Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by **5pm on Friday 1 June 2018** on **email:** TACommA@nice.org.uk

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Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.

The Appraisal Committee is interested in receiving comments on the following:

- has all of the relevant evidence been taken into account?
- are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- are the provisional recommendations sound and a suitable basis for guidance to the NHS?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**AstraZeneca**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	**Zavy Gabriel**

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Due to the technical nature of this response including tables, and figures, please see the response below.
2	

Insert extra rows as needed

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Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

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Dear Appraisal Committee Members,

AstraZeneca welcomes the opportunity to comment on this ACD.

To provide additional context to the response, we would like to outline to the committee the additional patient benefits of benralizumab, which will have a significant impact on patients' and their families' lives.

Burden of illness: As described in the ACD, severe eosinophilic asthma that is inadequately controlled despite SOC (high-dose ICS plus LABA) is a debilitating and distressing condition, with the risk of life-threatening exacerbations. Patients are often unable to work, and need help with day-to-day activities from carers/family members. Patients often require continuous treatment with oral corticosteroids (OCS), which can cause major side effects. These may incur a significant burden to patients and their families due to the need for additional hospital visits for monitoring and treatment of these side effects.

Benralizumab: Benralizumab is a new treatment option for patients with severe eosinophilic asthma. It is an anti-eosinophilic, humanised afucosylated monoclonal antibody, and has a different mechanism of action to mepolizumab and reslizumab. Data from the registrational trials have demonstrated that benralizumab reduces exacerbations, and lowers patients' exposure to and dependence on chronic OCS (oral corticosteroids) while still maintaining asthma control, as well as improving asthma symptoms and patient quality of life.

Significant patient benefits:

1. **Rapid onset of action, which we hypothesise translates into early patient-relevant benefits**
   Eosinophilic inflammation, stimulated by IL-5, plays an important role in the pathogenesis of asthma. By directly targeting IL-5Rα, benralizumab induces rapid and near complete depletion of eosinophils. Blood eosinophils are depleted by 100% within 24 hours of the first dose, and airway mucosal eosinophils by 96% at day 84 (Laviolette et al. 2013). Evidence from a post-hoc analysis of the SIROCCO and CALIMA trials has demonstrated that benralizumab improves morning lung function (measured as peak expiratory flow [PEF]) within the first week of treatment. Over the first week, mean PEF changes from baseline with benralizumab were 14.05 L/min (95% CI: 13.16–14.96) in SIROCCO and 14.58 L/min (95% CI: 13.71–15.83) in CALIMA. With corresponding placebo, mean changes were 7.16 L/min (95% CI, 6.28–7.99) and 8.75 L/min (95% CI, 7.91–9.65), respectively (Chupp et al. 2017).

   We hypothesise that the rapid depletion of eosinophils by benralizumab translates into patient-relevant benefits such as early improvements in lung function, symptoms, and quality of life, compared with current treatments. Studies are ongoing with earlier measurement timepoints than those reported in the pivotal clinical trials (first assessment at 4 weeks) to explore this hypothesis; for example, the randomised, controlled SOLANA trial (NCT02869438) is investigating the onset and maintenance of the effect of benralizumab on lung function, blood eosinophils, asthma control metrics, and quality of life over 12 weeks, in 222 patients with severe, uncontrolled, eosinophilic asthma. SOLANA is due to complete in August 2018.

Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

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2. **Less frequent dosing compared with existing biologics**

   The ACD states that "benralizumab could offer an easier method of administration compared with existing biologics". It refers to the less frequent dosing of benralizumab (every 8 weeks, except for every 4 weeks for the first 3 administrations), compared with mepolizumab and reslizumab (every 4 weeks). It mentions that the patient expert highlighted that benralizumab would be preferred by many patients as it involves less travel and fewer visits to specialist centres to receive regular biologic injections. The ACD also states that "The clinical experts considered this convenience in administration a 'step change'.

   We believe that the difference in dosing regimen could have a significant impact on patients' adherence to treatment, their quality of life, productivity, and on their families. For example, for patients living far from a severe asthma clinic who need a full day off work to travel to and from the clinic to receive a biologic, a patient on mepolizumab would require 13 days off work per year compared with 6-7 days per year for patients treated with benralizumab. Thus, treatment with benralizumab would allow patients access to specialist medical expertise whilst minimising the number of treatment administrations. Clinicians at the first appraisal committee meeting mentioned that some patients would refuse a biologic requiring every 4-week dosing (e.g. due to the number of days off work required), but would be more likely to accept benralizumab with every 8-week dosing. Benralizumab therefore meets a specific unmet need in this patient population, who prefer to receive biologic treatment less frequently.

   [redacted]

3. **Benralizumab is currently the only biologic available in a pre-filled syringe, thus facilitating administration at home or closer to home by a health-care professional**

   Benralizumab is available in a pre-filled syringe for subcutaneous injection, whereas mepolizumab is currently available as a powder for solution that requires reconstitution before it can be given subcutaneously; reslizumab is available as an intravenous infusion. Benralizumab's formulation and route of administration facilitates the administration of benralizumab by a healthcare professional at home, or closer to home than in the severe asthma clinic. When care closer to home is appropriate, this will reduce the number of times per year that a patient needs to attend a severe asthma clinic to receive a biologic injection, with potential patient benefits in reducing time off work and travel costs.

   [redacted]

Benralizumab for treating severe eosinophilic asthma [ID1129]

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4. **With a revised Patient Access Scheme, benralizumab is a cost-effective option versus SOC in the population where a recommendation is sought (patients with a blood eosinophil count of 300 cells per microlitre or more AND either 3 or more asthma exacerbations in the prior year or treatment with continuous oral corticosteroids over the previous 6 months)**

   This is the population where patients will benefit from the greatest efficacy of benralizumab as shown by key trials, with exacerbation reductions of [redacted] versus placebo based on pooled SIROCCO/CALIMA data, and a median percentage reduction in OCS dose from baseline of [redacted] for benralizumab compared with [redacted] for placebo in ZONDA. This population also aligns to clinical experts' expectations of where benralizumab is likely to fit into clinical practice in NHS England, and to the referral criteria within the NRAD report, which states that patients should be referred to specialist care after experiencing more than 2 exacerbations in a 1-year period.

   We urge the committee to consider the strong case for recommending benralizumab in this population to ensure that no patient (for which cost-effectiveness has been shown) misses out on the specific benefits of benralizumab.

Based on the above points and the technical information below, we ask the committee to grant a recommendation for benralizumab in the specified population (patients with a blood eosinophil count of 300 cells per microlitre or more AND either 3 or more asthma exacerbations in the prior year or treatment with continuous oral corticosteroids over the previous 6 months) to ensure that clinicians and patients have access to a treatment with specific patient benefits where there is high unmet need.

Your sincerely,

Laurent Abuaf

AstraZeneca UK Country President

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Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by **5pm on Friday 1 June 2018** on **email:** TACommA@nice.org.uk

Executive summary

We appreciate the opportunity to respond to this ACD, and kindly ask the committee to consider the following key points:

1. Revised Patient Access Scheme (PAS)

In response to the ACD, AstraZeneca has revised the PAS, such that the price of benralizumab is reduced to [redacted] per vial (previously [redacted]).

2. With a revised Patient Access Scheme, benralizumab is cost-effective versus SOC in the population where a recommendation is sought

Including a revised Patient Access Scheme and updated economic model inputs (aligned with the discussion at the committee meeting), we present new analysis showing that benralizumab is a cost-effective option for patients with severe asthma with 300+ eosinophils, AND either 3+ exacerbations in prior year OR receiving maintenance OCS (base-case population).

The ICER in the base-case population versus standard of care is £29,896.

3. The most relevant comparators are *both* mepolizumab and SOC

We agree with the committee that the most relevant comparators in this appraisal are *both* mepolizumab and standard of care; however, we do not agree that in the mepolizumab NICE-recommended population (300+ EOS; AND either 4+ exacerbations in prior year OR receiving maintenance OCS) that the *only* relevant comparator is mepolizumab as we believe that high dose ICS/LABA (standard of care) is still established NHS practice in England, and therefore *both* mepolizumab and standard of care are relevant comparators in this population.

We present an analysis of prescription data, which demonstrates that of those patients eligible for treatment with mepolizumab, only a minority are actually receiving mepolizumab. This shows that standard of care is still established NHS practice in England.

4. Matching-adjusted indirect comparison (MAIC) is the most appropriate method to estimate relative efficacy of benralizumab versus mepolizumab

Rationale: In the absence of head to head trial data, this method adjusts for differences between the benralizumab and mepolizumab trials to provide a more accurate estimate of relative efficacy to inform decision-making, which is not possible in a network meta-analysis (NMA).

[redacted].

Based on the data provided below and patient benefits described above, we ask the Committee to recommend benralizumab in the specified population (300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS), to ensure that clinicians and patients have access to a treatment with specific patient benefits where there is high unmet need.

Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by **5pm on Friday 1 June 2018** on **email:** TACommA@nice.org.uk

A. Comparators

The ACD for benralizumab for the treatment of severe asthma states "Mepolizumab is the relevant comparator for people who have had at least 4 exacerbations or are taking maintenance oral corticosteroids"

The NICE methods guide section 6.2.2 states that when selecting the most appropriate comparator(s), the Committee will consider:

- established NHS practice in England
- the natural history of the condition without suitable treatment
- existing NICE guidance
- cost effectiveness
- the licensing status of the comparator

Further, section 6.2.3 states "The Committee will normally be guided by established practice in the NHS when identifying the appropriate comparator(s)"

Given that mepolizumab gained a NICE recommendation recently (in 2017), the majority of patients eligible for mepolizumab are still receiving standard of care; thus, mepolizumab should not be considered to be the ***only*** established NHS practice for the treatment of these patients. Therefore, ***both*** standard of care and mepolizumab should be considered as comparators for these patients.

In order to corroborate this, AstraZeneca has undertaken an analysis of IQVIA prescriptions data to better understand the level of uptake of mepolizumab.

If we assume that one patient equates to one pack of mepolizumab for any given month then, as of March 2018, 1,677 (IQVIA, 2018) patients in the UK are currently receiving treatment with mepolizumab. The budget impact section of the manufacturer's submission for the NICE appraisal of mepolizumab estimates the number of eligible patients for mepolizumab to be 16,361* in 2018. Based on this, only 10.2% of eligible patients are being treated with mepolizumab and the remaining 89.8% are being treated with SoC (we recognise that a minority of these patients may also be receiving treatment with omalizumab or reslizumab). It should be noted that this population reflects the one originally submitted in the manufacturer's submission (≥150 eosinophils) rather than that within the final recommendation (≥300 eosinophils). If we revise this eligible population estimate through reducing the eligible population by an assumed one-third, to take account of this change in the eosinophil cut off, then this still shows that only 15.5% of eligible patients are being treated with mepolizumab (the remaining 84.5% being treated with SoC).

AstraZeneca approached 14 severe asthma centre lead consultants to ask for their views on the ACD including their views on this topic. Five of these consultants did not share their views with AstraZeneca (3 had a conflict of interest; 2 were on holiday). Of the 9 who shared their views, 8 consultants stated that the most relevant comparators for the mepolizumab-eligible population are both mepolizumab and SOC**.

For these reasons, we continue to present cost-effectiveness analysis vs. SoC in the base case population (300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS, and vs mepolizumab in the mepolizumab NICE-recommended population); we do not present cost-effectiveness analysis for benralizumab vs. SoC in patients with (exactly) 3 exacerbations in the prior year, who are not taking oral corticosteroids, a population eluded to in the ACD.

* note that this number applies to England and Wales while the prescriptions data comes from the UK as a whole –the derived percentage for mepolizumab may therefore be a slight overestimate and residual percentage a slight underestimate."

** All consultants gave written consent for AstraZeneca to include their views in the AstraZeneca response to the ACD within anonymised aggregate summaries of clinical opinion

B. Matching-adjusted indirect comparison (MAIC)

From the Committee meeting and the subsequent ACD, we understand the Committee's viewpoint that there is significant uncertainty associated with the relative treatment effects of benralizumab versus mepolizumab. However, we maintain that MAIC is the most appropriate approach to compare the relative treatment effect of benralizumab with mepolizumab in the absence of head-to-head studies and in line with NICE Decision Support Unit technical support document no. 18 (Phillippo 2016). A summary of the comparative advantages and limitations of NMA and MAIC to compare benralizumab with mepolizumab is presented in the table below.

Table 1: Key advantages and limitations of standard NMA and MAIC to assess the relative efficacy of benralizumab versus mepolizumab

Approach	Advantages	Limitations
MAIC	• Adjusts for differences between the benralizumab and mepolizumab trials by reweighting patients to provide a more accurate estimate of relative efficacy to inform decision-making (which is not possible in an NMA) • Uses individual patient data (IPD) for benralizumab and aggregate data for mepolizumab to use the largest data-set possible with the data available to AZ	• Differences in eligibility criteria for OCS reduction or discontinuation between the OCS-sparing trials could not be adjusted for using MAIC (this would also be the case in an NMA)
Standard NMA	• Enables a comparison of all three medicines (benralizumab, mepolizumab, and reslizumab), although limited by high heterogeneity so the results should not inform decision-making	• Differences between benralizumab and mepolizumab trials are not adjusted for, meaning the principle of exchangeability required for an NMA does not hold, and making it an inappropriate method • Very high level of heterogeneity meaning that results from the NMA would not provide a good estimate of relative effectiveness between the three medicines, and could misinform decision making • Would use aggregate data for both benralizumab and mepolizumab, so would not capitalise on IPD available to AstraZeneca for benralizumab

IPD: individual patient data; MAIC: matching-adjusted indirect comparison; NMA: network meta-analysis

If an NMA were to be conducted, there would be a very high level of heterogeneity that would be ignored in the analysis, meaning that results from the NMA would not provide a robust estimate of relative effectiveness between the three medicines, and could misinform decision-making. This is because the principle of exchangeability does not hold due to substantial differences between the benralizumab and mepolizumab trials.

The MAIC method adjusts for the differences between the benralizumab and mepolizumab trials, to give an estimate of relative efficacy that incorporates this known uncertainty, and so is a more appropriate guide to inform decision-making. We recognise that MAIC is associated with limitations such as the potential for the occurrence of extreme weights, but believe that these limitations are considerably outweighed by the advantage of adjusting for cross-trial differences.

In the MAIC analysis, [redacted]

The MAIC was conducted using ITT data from the trials, as the literature searches found no data for mepolizumab in the subgroup where it is NICE-recommended. We assumed that the relative treatment effect for benralizumab versus mepolizumab as derived from the MAIC in the full trial populations is generalisable to the mepolizumab NICE-recommended population. The relative difference between treatments was applied to the benralizumab data for the mepolizumab NICE-recommended population (300+ EOS; AND either 4+ exacerbations in prior year OR receiving maintenance OCS) to inform the economic model. Although this assumption is unverified, we have not identified a reason why the relative effect between benralizumab and mepolizumab would differ in the mepolizumab NICE-recommended population, or a better way to compare the two treatments.

In summary, we believe that MAIC is the most appropriate methodology to compare the relative effect of benralizumab and mepolizumab, given the limited data available at this time.

A more detailed description of the features and relative merits of NMA and MAIC is presented in Appendix 2, along with further details on how the MAIC results have been applied in the model. In-depth results of the MAIC are presented in Appendix 3.

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Consultation on the appraisal consultation document – deadline for comments by **5pm on Friday 1 June 2018** on **email:** TACommA@nice.org.uk

C. Model Inputs

In this section, we outline the assumptions that have been employed in the revised cost-effectiveness analysis.

Revised Patient Access Scheme (PAS)

In response to the ACD, AstraZeneca has revised the PAS, such that the price per vial of benralizumab is reduced to [redacted] per vial (previously [redacted]).

Mortality

Whilst we agree with the ERG that asthma-related mortality has decreased in the UK since 2007 when Watson et al was published, we are concerned that data on mortality from a patient cohort of all asthma severities may not be the most appropriate to apply to a severe asthma population. However, in the absence of any recent data specific to this population, we have included the ERG's scaling of mortality risk in the economic model, but we consider this to be a conservative assumption.

Percentage of patients on mOCS at baseline

The ERG base case includes a figure of 41.7% of patients being on mOCS at baseline, for both populations, which is sourced from Heaney et al. However, during the discussion at the committee meeting it was clear that this figure, based on a population of all severe asthmatics (i.e. not taking into account eosinophils or exacerbation history) would be an underestimate. We believe that our original figure of 54.1%, which is based on a robust, sub-analysis of UK RWE data is the most appropriate to use in the base case population (300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS).

This is further validated as the clinical experts at the meeting suggested that a figure of 60% would be more appropriate for the mepolizumab NICE-recommended population. It follows from this that if 41.7% of all severe asthmatic patients are on mOCS, and 60% of those patients who meet the criteria for the mepolizumab NICE-recommended population are on mOCS, then the percentage of patients who are on mOCS in the base case population (300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS) must lie between these two figures.

As previously mentioned, the clinical experts at the meeting suggested that a figure of 60%, which is lower than the 78% from the robust UK RWE in the relevant patient population, would be more appropriate for the mepolizumab NICE-recommended population. To provide a conservative estimate of cost effectiveness, we have included the 60% figure in our revised analyses, although we believe this may be an underestimate.

Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by **5pm on Friday 1 June 2018** on **email:** TACommA@nice.org.uk

Administration time

During the discussion at the committee meeting, the subject of administration time for benralizumab and mepolizumab was raised. The ERG had made the assumption in their base case that it would take the same amount of time to administer both mepolizumab and benralizumab; however, the clinical experts stated that it would be more appropriate to assume that mepolizumab took 15 minutes longer than benralizumab to administer, due to the need to reconstitute mepolizumab prior to administration.

We have therefore assumed a 15-minute administration time saving for benralizumab versus mepolizumab in our revised base case.

Summary of model inputs

Table 2: Summary of economic model inputs

Input	Value	Justification
Price of benralizumab	[redacted] per vial	Revised PAS
Mortality associated to Asthma exacerbations	Scaled by 0.4	As per ERG base case
% patients on mOCS	54.1% in the base case population 60% in the mepolizumab NICE recommended population	As per UK RWE As per committee meeting clinical expert opinion and ACD document
Administration time	5 minutes for benralizumab 20 minutes for mepolizumab	As per committee meeting clinical expert opinion
Clinical effectiveness of benralizumab vs mepolizumab	As per MAIC results	MAIC is the most appropriate way of assessing relative clinical effectiveness between these two medications (see section 2)
Treatment discontinuation	Set at 0.0041 per cycle	As per ERG base case
All other model inputs remain as in manufacturer submission base case		

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D. Cost Effectiveness Results

Incorporating the modelling assumptions mentioned above results in an ICER versus standard of care in the base case population (300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS) of £29,896, as shown in Table 3 below.

Table 3: Cost effectiveness results vs SoC in Base Case population

Scenario		Total cost	Δ cost	Total QALYs	Δ QALYs	ICER
Base Case	Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£29,896
	SoC	[redacted]		[redacted]		

Table 4 below shows the revised cost effectiveness analysis vs mepolizumab in the mepolizumab NICE recommended population (300+ EOS; AND either 4+ exacerbations in prior year OR receiving maintenance OCS).

Table 4: Cost effectiveness results vs mepolizumab in mepolizumab NICE reccommended population*

Scenario		Total cost	Δ cost	Total QALYs	Δ QALYs	ICER
Base Case	Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
	Mepolizumab	[redacted]		[redacted]		

*Benralizumab net price vs mepolizumab list price

We submit an updated CUA model alongside this ACD response.

Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by **5pm on Friday 1 June 2018** on **email:** TACommA@nice.org.uk

Appendix 1 – Additional Matched Adjusted Indirect Comparison (MAIC) Tables

Table 5: Comparison of baseline characteristics of patients included in benralizumab and mepolizumab studies

The highlighted cells indicate differences across benralizumab and mepolizumab trials

Characteristics	SIROCCO		CALIMA		MENSA			DREAM	
Population	Overall		HD ICS subgroup		Overall			Overall	
	BENRAQ 8W N=398	Placebo N=407	BENRA Q8W N=364	Placebo N=370	MEPO 100 mg SC N=194	MEPO 75 mg IV N=191	Placebo N=191	MEPO 75 mg IV N=153	Placebo N=155
Age, years	47.6 (14.5)	48.7 (14.9)	50.1 (13.3)	49.8 (14.3)	51.2 (14.55)	50.0 (14.03)	49.2 (14.26)	50.2 (11.3)	46.4 (10.8)
Gender, % males	36.7	33.9	38.2	40.3	40.0	45.0	44.0	32.0	37.0
White, % patients	72.1	74.2	85.2	86.8	77.0	79.0	77.0	91.0	90.0
Black, % patients	3.8	3.9	3.6	3.2	4.0	3.0	2.0	3.0	4.0
Asian, % patients	12.6	12.3	11.0	10.0	18.0	17.0	20.0	5.0	6.0
Other, % patients	11.6	9.6	0.3	0.0	1.0	1.0	1.0	1.0	0.0
Body mass index	28.21 (6.18)	28.93 (7.07)	29.0 (6.5)	29.25 (6.54)	27.60 (5.58)	27.68 (5.68)	28.04 (5.58)	28.4 (6.0)	28.3 (6.1)
FEV1 predicted (%)	56.1$	56.6$	56.9	57.5	59.3	61.4	62.4	60$	59$
Morning PEF (L/min)	233.12	230.83	241.85	242.16	255.3	268.6	277	-	-
FEV1/FVC (%)	65	66	64	65	66	67	67	68	67
FEV1 pre-bronch. (L)	1.68	1.66	1.72	1.76	1.73	1.85	1.86	1.81$	1.90$
Reversibility (%)	27.2	25.5	25.1	27.2	27.9$	25.4$	27.4$	22.6^	26.8^
ACQ scores**	2.8	2.87	2.82	2.73	2.26	2.12	2.28	2.2	2.5
Exacerbations in previous year	2.8	3	2.7	2.8	3.8	3.5	3.6	>3~	>3~
2 exacerbations in previous year (% patients)	63.3	60	62.9	63.5	38	43	47	46	42
≥3 exacerbations in previous year (% patients)	36.68	40	36.81	36.49	61.86	57.07	52.88	54	57
Never smokers (% patients)	82.2	80.6	78.02$	78.92$#	74$#	73$	70$	80$	78$
OCS use (% patients)	17.8	16.2	10.71$	11.08$#	27$#	25$	23$	30.07$	29.03$
EOS ≥300 cells/µL (% patients)	67.08	65.6	65.6	67.02	43.2	41.3	41.8	56.2	45.16
EOS <300 cells/µL (% patients)	32.9	34.3	34.3	32.9	54.6	55.4	56.5	43.7	54.8
EOS (cells/µl)	369.8	456.5	463.4	490.8	290*	280*	320*	250*	280*
IgE levels	-	-	-	-	149.72*	180.32*	150.12*	-	-
Atopic status	61.3	56.5	61.5	63.0	-	-	-	51.0	52.0
Nasal polyps	23.2	23.2	16.8	18.1	14.4	16.7	17.2	7.0	10.0

The highlighted cells indicate differences across benralizumab and mepolizumab trials.
"Overall" for SIROCCO, MENSA and DREAM refer to a population receiving high-dose ICS. The data in the table represent mean (SD) values unless otherwise indicated. **ACQ-6 in SIROCCO, CALIMA, and DREAM; ACQ-5 in MENSA. $The data is extracted from the respective publications. All other values are extracted from the respective CSR; #Calculated from the reported subgroup data. ~Calculated from the reported frequency of exacerbations; ^Data reported at screening visit; *Geometric means

Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by **5pm on Friday 1 June 2018** on **email:** TACommA@nice.org.uk

ACQ: Asthma Control Questionnaire; BENRA: Benralizumab; CSR; Clinical study report; EOS: Eosinophil; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; HD: High-dose; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; IV: Intravenous; MEPO: Mepolizumab; OCS: Oral corticosteroid; PEF: Peak expiratory flow; Q8W: every eight weeks; SD: Standard deviation

Table 6: Comparison of baseline characteristics of patients in the ZONDA and SIRIUS trials

Characteristics	ZONDA		SIRIUS	
	Overall		Overall	
	BENRA Q8W	Placebo	MEPO 100 mg SC	Placebo
Age (years)	52.9 (10.1)	49.9 (11.7)	49.8 (14.1)	49.9 (10.3)
Males (% patients)	35.6	36.0	36.0	55.0
BMI (kg/m2)	30.2 (6.5)	28.7 (5.2)	27.8 (5.9)	29.5 (6.1)
Pre-bronchodilator FEV1 predicted (%)	59.0 (17.9)	62.0 (16.5)	59.6 (17.0)	57.8 (18.5)
Pre-bronchodilator FEV1/FVC (%)	59.0 (12.0)	62.0 (13.0)	63.0 (12.4)*	61.0 (11.7)*
Pre-bronchodilator FEV1 (L)	1.8 (0.64)	1.9 (0.7)	1.9 (6.6)	2.0 (8.2)
Reversibility (%)	25.1 (19.0)	23.2 (18.0)	24.9 (19.3)	23.7 (18.6)
ACQ scores	2.4 (1.2)	2.7 (0.9)	2.2 (1.3)	1.99 (1.2)
Mean number of exacerbation in previous year	3.1 (2.8)	2.5 (1.8)	3.3 (3.4)	2.9 (2.8)
0 exacerbations in previous year (% patients)	0	0	17.0	15.0
1 exacerbations in previous year (% patients)	28.8	32.0	16.0	17.0
≥2 exacerbations in previous year (% patients)	71.2	68.0	67.0	68.0
Never smokers (% patients)	83.6	77.3	59.0	62.0
OCS dose (prednisolone equivalent), mg/day	14.3 (7.8)	14.2 (6.4)	12.4 (7.2)	13.2 (6.3)
Local EOS count (cells/µL)	509.0 (320.2)	656.0 (589.0)	413.0 (386.2)	347.0 (303.3)
Omalizumab use (% patients)	12.3	10.7	33.0	33.0
Nasal polyps (% patients)	27.4	37.3	23.0	26.0

Highlighted cells indicate differences between the benralizumab and mepolizumab trials
*The data are extracted from the respective publication. All other values are extracted from the respective CSRs
The data in the table represent mean (SD) unless otherwise indicated
ACQ: Asthma Control Questionnaire; BENRA: Benralizumab; BMI: Body mass index; CSR: Clinical study report; EOS: Eosinophil; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; MEPO: Mepolizumab; OCS: Oral corticosteroid; Q8W: every 8 weeks; SC: Subcutaneous; SD: Standard deviation

Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by **5pm on Friday 1 June 2018** on **email:** TACommA@nice.org.uk

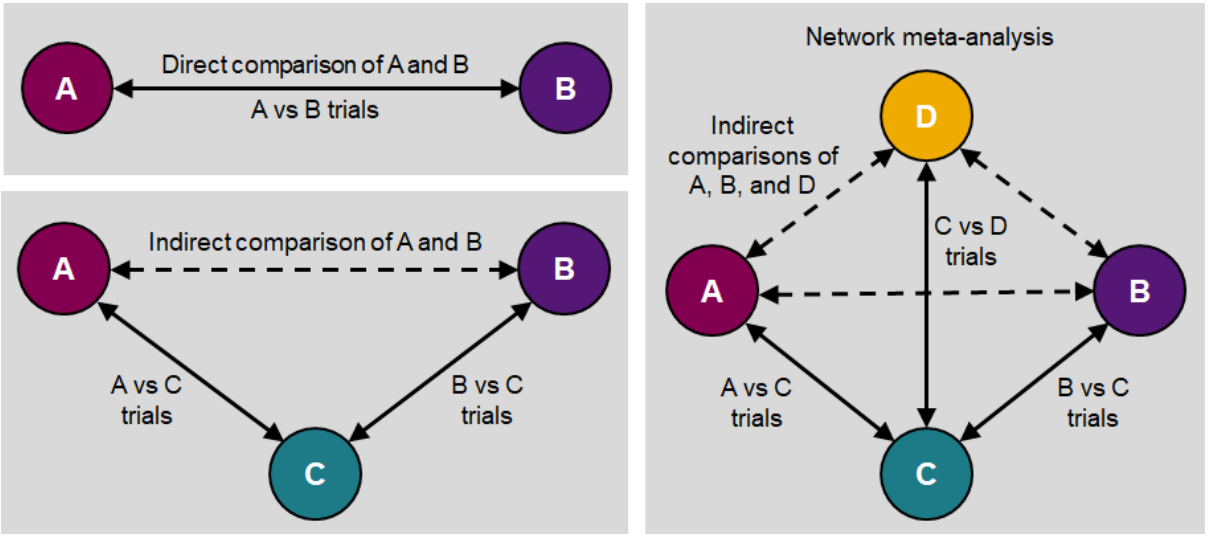
Appendix 2 – MAIC vs NMA – further information

We present further discussion below which seeks to demonstrate that not only is the MAIC methodology the most appropriate to use when deriving the relative treatment effects of benralizumab versus mepolizumab, but that the way in which we have applied these results in the economic model is also robust.

What is indirect treatment comparison (ITC) and network meta-analysis (NMA), and when do these methods support decision-making?

In the absence of head-to-head trials between treatments of interest, an indirect treatment comparison (ITC) can provide evidence for comparative effectiveness. ITC uses data from separate studies to compare treatments, in contrast to a direct comparison within a randomised controlled trial (**Error! Reference source not found.**). Network meta-analysis (NMA) is a type of indirect comparison where the evidence base consists of more than two RCTs connecting more than two interventions.

Figure 1: Structure of direct and indirect treatment comparisons and NMA



One of the main requirements of a standard ITC is that the included studies are similar in terms of study, disease, and patient characteristics, in order to determine the true treatment effect of each intervention. This is because standard ITCs assume that treatment effect is constant (i.e. exchangeable) across studies. NMA is also based on the same principle of exchangeability.

Conclusion: When studies are similar, a standard ITC or NMA can support decision-making in the absence of head-to-head evidence

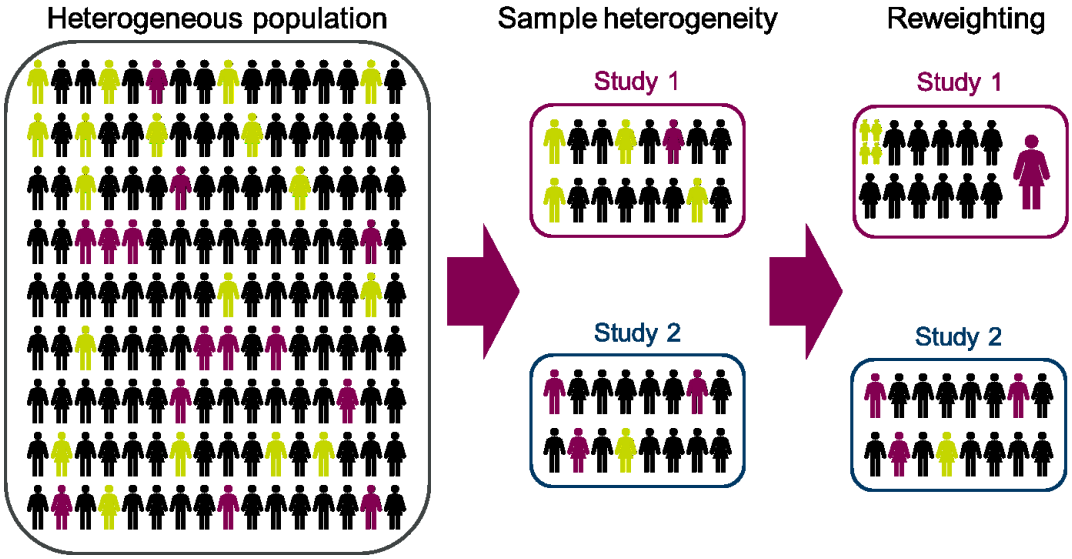
NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by **5pm on Friday 1 June 2018** on **email:** TACommA@nice.org.uk

What is matching-adjusted indirect comparison (MAIC), and when is this method more appropriate than standard ITC?

In cases where between-trial differences are too large to conduct a robust standard ITC/NMA, exchangeability concerns can be addressed through one of several approaches: 1. reweight patients in one study to match the other (including matching-adjusted indirect comparison [MAIC]); 2. model differences in one study and simulate the effects in the other (termed simulated treatment comparison [STC]); or 3. conduct a patient-level meta-analysis (which requires individual patient-level data for all medicines). In cases where individual patient-level data are available for one intervention but only aggregate data are available for the other, reweighting of patients helps to make the studies more comparable while still using real (rather than simulated) data. Matching-indirect treatment comparison (MAIC) is one such reweighting approach, adjusting for differences between populations by applying weights to patients in the intervention trial so that the average characteristics match the comparator population (**Error! Reference source not found.**).

Figure 2: The re-weighting approach used in a MAIC



The main advantage of the MAIC approach is therefore the ability to adjust for trial differences, which would not otherwise be possible using standard ITC/NMA, or in the absence of patient-level data for both intervention and comparator. MAIC is becoming an increasingly recognised approach in light of this methodological advantage, with a growing body of literature and increasing use in HTA submissions, particularly since the publication of NICE Decision Support Unit guidance on the use of population-adjusted ITCs in 2016, which includes guidance on using MAIC in NICE submissions. Please note that based on analysis of information from appraisal summary documents, 13 NICE manufacturer submissions have included the MAIC methodology since 2014.

Conclusion: When there are differences between the studies in baseline characteristics which may have an impact on the treatment effects, a MAIC can support decision making.

Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by **5pm on Friday 1 June 2018** on **email:** TACommA@nice.org.uk

Limitations of MAIC

Although MAIC is associated with advantages over standard NMA when substantial between-trial differences exist, the results are still subject to certain limitations. For example, the occurrence of extreme weights for some patients while matching can lead to decreased statistical power to detect differences between the treatments.

Why is MAIC the best method to estimate the relative effectiveness of benralizumab compared with mepolizumab?

There are no head-to head-trials comparing benralizumab and mepolizumab. Based on the evidence identified from the systematic literature review of severe asthma biologics, the benralizumab and mepolizumab trials vary substantially in their eligibility criteria, baseline characteristics, and disease severity of the patient population, these differences are presented in appendix 1 at the end of this document. Specifically, key differences related to baseline eosinophil levels, the definition of high-dose ICS, prior exacerbation history, proportion of OCS use at baseline, ACQ-6 scores, and treatment duration. Similarly, the benralizumab and reslizumab trials varied in terms of sample size, disease severity, medium-dose ICS cut-off, exacerbation history in previous year, and baseline EOS count. These differences meant that a standard ITC (benralizumab versus mepolizumab, and benralizumab versus reslizumab) or an NMA combining all relevant studies for all three medicines (benralizumab, mepolizumab, and reslizumab) in a single evidence network was not feasible.

Limitations of the MAIC for benralizumab versus mepolizumab

Differences in eligibility criteria for OCS reduction or discontinuation between the OCS-sparing trials could not be adjusted for using MAIC, and the results of the OCS-sparing trials should be interpreted with due caution (this would also be the case in an NMA where no adjustments are made).

Method used to apply the MAIC results to the economic model

The MAIC was conducted using ITT data from the trials, as the literature searches found no data for mepolizumab in the subgroup where it is NICE-recommended. We assumed that the relative treatment effect for benralizumab versus mepolizumab as derived from the MAIC in the full trial populations is generalisable to the mepolizumab NICE-recommended population, to inform the decision problem. The relative difference between treatments was applied to the benralizumab data for the mepolizumab NICE-recommended population (300+ EOS; AND either 4+ exacerbations in prior year OR receiving maintenance OCS) to inform the economic model.

Although this assumption is unverified, we have not identified a reason why the relative effect between benralizumab and mepolizumab would differ in the mepolizumab NICE-recommended population, or a better way to compare the two treatments.

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by **5pm on Friday 1 June 2018** on **email:** TACommA@nice.org.uk

We consider it reasonable to assume that the relative efficacy between the drugs will be the same in the all-comers trial population as in the more severe sub-group; and we have not identified any reasons/clinical rationale against this assumption. Further, since both drugs show greater efficacy in more severe patients, i.e., as EOS increases and exacerbation frequency increases, we would expect the relative difference in effect seen in the ITT populations to remain in place in the more severe sub-group. We validated this assumption with a UK clinician, who confirmed that the relative difference between benralizumab and mepolizumab in the ITT population could be assumed to be generalisable to the more severe subgroup. This approach is also in line with the assumptions made in both of the previous appraisals in severe asthma where mepolizumab and reslizumab were compared to omalizumab (TA431 and 479).

It should be noted that a NMA methodology would not prevent this limitation as to our knowledge, there is no published data for mepolizumab in the subgroup where it is NICE recommended.

In conclusion, we believe that we have used the best method to estimate and apply relative effectiveness of benralizumab vs mepolizumab, considering the limited data available in the NICE recommended population at this time.

Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by **5pm on Friday 1 June 2018** on **email:** TACommA@nice.org.uk

Appendix 3 – MAIC (Matched Adjusted Indirect Comparison) results – further information

Overview:

Table 7: Summary of MAIC results for SIROCCO/CALIMA versus MENSA/DREAM

Studies	Endpoint comparison	Benralizumab vs. mepolizumab* (matched): RR (95% CI)	
SIROCCO/CALIMA vs. MENSA/DREAM	Annualised rate of clinically significant exacerbations	[redacted]	[redacted]
	FEV_1 at week 32	[redacted]	[redacted]
	Annualised exacerbation rate leading to ER/hospitalisation	[redacted]	[redacted]

[redacted]

Table 8: Summary of MAIC results for ZONDA versus SIRIUS

Studies	Endpoint comparison	Benralizumab vs. mepolizumab* (matched)	
ZONDA vs. SIRIUS	Percentage reduction in OCS dose, mean difference (95% CI)	[redacted]	[redacted]
	Patients with complete reduction in OCS dose, OR (95% CI)	[redacted]	[redacted]
	Annual exacerbation rate reduction/ clinically significant exacerbations, RR (95% CI)	[redacted]	[redacted]

[redacted]

In-depth MAIC results for SIROCCO/CALIMA versus MENSA/DREAM trials

Figure 3: Base case MAIC results for clinically significant exacerbations (≥ 880 µg FP daily)

[redacted]

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Figure 4: Base case MAIC results for exacerbations resulting in ER/hospitalisation (≥ 880 µg FP daily)

Figure 5: Base case MAIC results for change from baseline in pre-bronchodilator FEV_1 (L) (≥ 880 µg FP daily)

In-depth MAIC results for ZONDA versus SIRIUS trials

Figure 6: Base case MAIC results for percent reduction in OCS dose at 24 weeks

Figure 7: Base case MAIC results for proportion of patients with complete reduction in OCS dose at 24 weeks

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Figure 8: Base case MAIC results for annual rate of clinically significant exacerbations

Benralizumab for treating severe eosinophilic asthma [ID1129]

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Appendix 4

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References

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Consultation response on the appraisal of Benralizumab for treating severe eosinophilic asthma

Key points

- Current treatments do not work well for severe asthma, and often result in unpleasant side effects such as sleep disturbance and increased appetite and long-term co-morbidities such as diabetes and osteoporosis
- A disproportionate number of the people that die from asthma have severe asthma so the severe asthma patient group is one with a significant unmet need
- Benralizumab has the potential to control the symptoms of people with severe, eosinophilic asthma and reduce their use of the health care system, so Asthma UK is urging NICE to approve the use of Benralizumab to treat severe eosinophilic asthma

Response on behalf of Asthma UK

Asthma is one of the most prevalent long-term conditions in the UK, with 5.4 million people currently receiving treatment. Severe asthma affects nearly 5% of people with asthma – around 250,000 people in the UK, of whom a subgroup of around 40% will have an eosinophilic phenotype. The National Review of Asthma Deaths highlighted that almost 40% of those who died had severe asthma[1].

Though existing biologics have offered relief of symptoms to some, they are limited in that they are only made available to a specific sub-population. As such, the approval of a new biologic offers an opportunity to help more people with severe asthma.

Consequences of the current decision not to approve Benralizumab

A. Impact on the lives of people with severe asthma:
   - There are only limited treatment options available to people with severe eosinophilic asthma.
   - Oral corticosteroids are not very effective at controlling severe asthma and they can have toxic and debilitating side-effects
   - Despite adhering to current recommended asthma treatments, symptoms can persist and patients' asthma can remain uncontrolled, putting them at risk of potentially life-threatening attacks as well as significantly disrupting their quality of life.
   - Benralizumab could provide an (additional) alternative option for people with severe eosinophilic asthma who respond poorly to oral steroids.

B. Cost to the health care system:
   - People with uncontrolled severe asthma cost four times as much as the average patient[2].
   - Approving an additional biologic to help with the management of severe asthma will reduce the number of exacerbations and A&E visits or hospital admissions

[1] M. Levy et al., 'Why Asthma Still Kills: The National Review of Asthma Deaths (NRAD)', Report or Working Paper, 6 May 2014, https://www.rcplondon.ac.uk/projects/national-review-asthma-deaths.
[2] Marjan Kerkhof et al., 'Healthcare Resource Use and Costs of Severe, Uncontrolled Eosinophilic Asthma in the UK General Population', *Thorax*, 16 September 2017, thoraxjnl-2017-210531, https://doi.org/10.1136/thoraxjnl-2017-210531.

Contact details

[redacted] - Policy Officer, Asthma UK

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[redacted]

Benralizumab for treating severe eosinophilic asthma [ID1129]

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`	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	GSK UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We agree with the Committee's conclusion that the clinical effectiveness of benralizumab versus mepolizumab through a matching adjusted indirect treatment comparison is highly uncertain and that the comparison is not considered robust. We believe: a) there are instances where relevant evidence has been excluded from consideration in this comparison b) the result of the matching-adjusted indirect treatment comparison may be misleading because of the way in which matching was handled as well as the exclusion of a treatment effect modifier, the Asthma Control Questionnaire. c) the interpretation and application of the results of the matching-adjusted indirect comparison to more severe sub-groups cannot be assumed based on available published evidence. Substantiation of this is made in the following comments below.
2	*Identification of the relevant evidence to inform the Matching-Adjusted Indirect Comparison of benralizumab vs. mepolizumab* We do not believe that evidence from DREAM should have been included as part of the basecase evidence for mepolizumab for the matching-adjusted indirect treatment comparison (or if it was, it should have been included as well as MUSCA – see comment 3) • Not all patients in the DREAM study (Phase IIb) meet the criteria for severe eosinophilic asthma due to underlying differences in the study inclusion criteria between DREAM and MENSA. While this was accounted for, by excluding inappropriate patients, in the analyses GSK submitted to NICE as part of the appraisal of mepolizumab, it was not, in this matching-adjusted indirect comparison. • The licensed dose and administration for mepolizumab is 100mg 4-weekly sub-cutaneous (SC) injection which was not studied in DREAM. We acknowledge the bio-equivalence of 75 mg IV to 100 mg SC, however this is not reason enough for inclusion of DREAM data in the basecase matching-adjusted indirect comparison, given the differences in the study inclusion criteria's (and given exclusion of the MUSCA data). • We believe that inclusion of the 75 mg IV mepolizumab data from DREAM, into the matching-adjusted indirect comparison would potentially over-inflate the numerical advantage shown for benralizumab.
3	*Identification of the relevant evidence to inform the Matching-adjusted indirect comparison of benralizumab vs. mepolizumab* We believe that the MUSCA study, studying the licenced mepolizumab dose (100mg SC) and an appropriate severe eosinophilic asthma population, should have been included as relevant evidence for mepolizumab in the basecase matching-adjusted indirect comparison. By excluding it, the numerical advantage for benralizumab is improved as concluded by the Committee in the ACD. • MUSCA (Chupp et al., 2017), a Phase 3b, placebo controlled, double blind, parallel group, multicentre study, was designed to assess the effect of add-on mepolizumab on disease-specific health related quality of life. • The primary efficacy end point was the mean change from baseline in St. Georges Respiratory Questionnaire at week 24. Other end points (all measured at week 24)

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	included mean change from baseline in Asthma Control Questionnaire (v5) and annual rate of clinically significant exacerbations. • Therefore, MUSCA measured outcomes of interest to the matching adjusted indirect comparison • Even though the primary end point of MUSCA was the change from baseline in the St. Georges Respiratory Questionnaire at week 24, this does not mean the study was not powered to detect differences in efficacy as suggested by AZ. For example, in MENSA (Ortega et al., 2014), it was estimated that with 180 patients in each group, the study would have a power of 90% to detect a 40% decrease in the exacerbation rate. In MUSCA (Chupp et al., 2017), there were 277 on the placebo arm and 274 on the mepolizumab arm i.e. sufficient power to detect differences in efficacy. • More importantly, the recruited population to MUSCA most closely matches the populations recruited to the benralizumab trials, SIROCCO (Bleecker et al., 2016) and CALIMA (Fitzgerald et al., 2016). • For example, the number of exacerbations in the previous 12 months for the intent to treat population at baseline was reported as: ○ SIROCCO (Bleecker et al., 2016) ▪ n=1204, 2.9 (SD 1.69) ○ CALIMA (Fitzgerald et al., 2016) ▪ n=1091, 2.7 (SD 1.62) ○ MUSCA (Chupp et al., 2017 and https://www.gsk-clinicalstudyregister.com/files2/gsk-200862-clinical-study-report-redact.pdf) ▪ n=551, 2.8 (SD 1.75) ○ MENSA (Ortega et al., 2014) ▪ n=576, 3.6 (SD 2.6) ○ DREAM (Pavord et al., 2012) ▪ n=616, 3.6 (SD 3.0) • Although the study duration of MUSCA was relatively short (24 weeks), for outcomes of interest defined by ratios, such as exacerbation rate ratios, study duration becomes less relevant. Further, MENSA was not substantially longer at 32 weeks and therefore we do not believe the reason for excluding MUSCA from the basecase matching adjusted indirect comparison is suitably substantiated. Further, the long-term efficacy of mepolizumab have been demonstrated through extension studies.
4	*Identification of the relevant evidence to inform the indirect comparison of benralizumab vs. mepolizumab* There are other published data for mepolizumab excluded from the indirect comparison which would have supported better matching of benralizumab and mepolizumab and could have directed towards an alternative indirect comparison approach. • AZ stated that evidence pertaining to the efficacy of mepolizumab in the NICE recommended population was limited (baseline or historic >=300 eosinophils /µL and either >= 4 exacerbations in the previous 12 months or continuous OCS use for the past 6 months). • AZ stated they identified one abstract reporting a post-hoc analysis of the MENSA study in patients with >=300 eosinophils /µL and 3 exacerbations in the prior year which demonstrated increased efficacy relative to the overall MENSA population. • However, AZ chose not to include this in the indirect comparison stating the data for the sub-group were available for only one, of the two mepolizumab exacerbation trials, MENSA (and not DREAM). • We disagree that this is reason to exclude the abstract. ○ The abstract still presents relevant evidence to the decision problem and could have been included in a sensitivity analysis to the indirect comparison.

	▪ The rate ratio of mepolizumab vs. placebo for exacerbations among patients with a history of >=3 exacerbations in the past year and eosinophils of >=300 cells/μL at baseline was 0.34 (95% CI 0.23, 0.51) (Yancey et al., 2017). This compares to a rate ratio of benralizumab vs. placebo of 0.45 (95% CI 0.34-0.60) for the same population reported in the meta-analysis of SIROCCO and CALIMA (Fitzgerald et al., 2018, Table 6). • There is also a published meta-analysis of the MENSA and DREAM mepolizumab studies (Ortega et al., 2016). We disagree with the ERG's conclusion that this secondary analysis was appropriately excluded by AZ. This meta-analysis included an analysis of the reduction in exacerbation rate stratified by baseline blood eosinophil count which could have made an indirect comparison through other methods possible. o The rate ratio of mepolizumab vs placebo for reduction in exacerbations among patients with baseline eosinophils of >=300 cells/μL was 0.41 (95% CI 0.33, 0.51) (Ortega et al., 2016, Table 2). Further this rate ratio included a less severe population; patients with < 1.5 Asthma Control Questionnaire score (which were excluded from SIROCCO and CALIMA) and >= 2 exacerbations in the last year. It is likely that this rate ratio would have improved further in favour of mepolizumab in the more severe AZ proposed asthma population. The rate ratio was also reported for MENSA (0.39 [95% CI 0.28, 0.55]) and DREAM (0.42 [95% CI 0.31, 0.56]) separately.
5	*The method of matching on baseline characteristics (as part of the matching adjusted indirect comparison) may have biased the results numerically in favour of benralizumab* Asthma Control Questionnaire version 6 (ACQ-6) is clearly a treatment effect modifier for benralizumab and yet this was not selected for matching with the mepolizumab population. • Table 40 in the ERG Report presents a summary of the selection of variables for matching to inform the matching-adjusted indirect comparison and shows that ACQ-6 is clearly a treatment effect modifier. This is further supported by the meta-analysis looking at predictors of enhanced response with benralizumab (Fitzgerald et al., 2018, Figure 2). • Table 40 of the ERG report states that AZ did not select ACQ-6 for matching because different scale versions were used in the mepolizumab studies (ACQ-6 was used in DREAM and ACQ-5 was used in MENSA) • We believe that matching could still have been performed. o The use of different versions of the ACQ in the different clinical trials (ACQ-7 in the reslizumab trials, ACQ-6 in the benralizumab trials and ACQ-5 and ACQ-6 in the mepolizumab trials) is a limitation; however, a number of validation studies have been published, including by the developers of the instruments, showing that all ACQ versions have similar psychometric properties, that the results with either instrument is very similar in large studies, including for change, and conclude that the three versions can be used without loss of validity or change in interpretation. o In accordance with this point, the mean ACQ-6 score for the ITT at baseline from DREAM was 2.4 (SD 1.1) (Pavord et al.,2012) and the equivalent mean ACQ-5 score is 2.4 (SD 1.1) (Ortega et al., 2016). Compared with baseline mean ACQ-6 scores for SIROCCO 2.81 (SD 0.93) and CALIMA (2.76 SD 0.93) (FitzGerald et al., 2018) o We therefore believe it is possible to match on ACQ, a key treatment modifier and in doing so, this would have favoured mepolizumab.
6	*The method of matching on baseline characteristics (as part of the matching adjusted indirect comparison) may have biased the results numerically in favour of benralizumab* Matching of baseline eosinophil counts is based on two categories, ≥ 300 cells/μL and < 300 cells/μL.

	Clinically and methodologically, it would be appropriate to consider using more bands, especially given eosinophils is a very strong predictor of response. • Different clinicians define severe eosinophilic asthma by different eosinophil levels and these levels can vary based on clinical patient history. • Moreover, we know that increased baseline eosinophils results in increased response to mepolizumab and benralizumab. • For mepolizumab, the rate ratio for exacerbations, across a range of thresholds is reported (< 150 cells/μL, 150-<300 cells/μL, 300-<500 cells/μL and ≥ 500 cells/μL) which could have been matched with the benralizumab data. The resultant estimate for SIROCCO/CALIMA after adjustment may differed as a result of looking at different blood eosinophil categories.
7	*The method of matching on baseline characteristics (as part of the matching adjusted indirect comparison) may have biased the results numerically in favour of benralizumab* Matching on previous exacerbations in the last 12 months is based on two categories, 2 and >2. Clinically and methodologically, it might have been more appropriate to explore using a greater number of bands especially given clinician's views of patients with an increasing number of previous exacerbations. For example, a patient having experienced 3 exacerbations is different to another who may have experienced 5 exacerbations etc. For both mepolizumab and benralizumab studies, the proportion of patients with 2, 3, and >3 exacerbations in previous year was available. Matching based on these categories may have yielded very different results.
8	*Interpretation of the matching adjusted indirect comparison results to more severe sub-groups* We disagree with the assumption that the relative treatment effects obtained from the matching adjusted indirect comparison can be carried forward to more severe patient subgroups. • AZ claims that they have not identified a reason why the relative treatment effect between benralizumab and mepolizumab would differ in the mepolizumab NICE-recommended population and that the relative treatment effect for benralizumab and mepolizumab as derived from the matching adjusted indirect comparison from the full trial populations can be applied to data for the mepolizumab NICE-recommended population. • There is published evidence to support why the relative treatment effect of benralizumab cannot be assumed to apply to more severe sub-populations. ○ The published meta-analysis of MENSA and DREAM (Ortega et al., 2016) clearly shows there is a dose response for add-on mepolizumab with increasing eosinophils at baseline. The reported rate ratio of mepolizumab vs. placebo for baseline eosinophils (EOS) is as follows: ▪ ≥ EOS 150 cells/μL is 0.48 (95% CI 0.39-0.58) ▪ ≥ EOS 300 cells/μL is 0.41 (95% CI 0.33-0.51) ▪ ≥ EOS 400 cells/μL is 0.34 (95% CI 0.27-0.44) ▪ ≥ EOS 500 cells/μL is 0.30 (95% CI 0.23-0.40). ○ The strength of this finding for mepolizumab is in contrast to that reported in the meta-analysis of the benralizumab studies (Fitzgerald et al., 2018). The reported rate ratio of benralizumab vs. placebo for baseline EOS is as follows: ▪ ≥ EOS 150 cells/μL is 0.63 (95% CI 0.53-0.74) ▪ ≥ EOS 300 cells/μL is 0.57 (95% CI 0.47-0.69) ▪ ≥ EOS 450 cells/μL is 0.50 (95% CI 0.38-0.64) ○ Published treatment effects estimate for mepolizumab (Ortega et al. 2016) and benralizumab (Fitzgerald et al., 2017) are presented below. With increasing eosinophils thresholds, there appears to be a trend towards further separation between mepolizumab and benralizumab in favour of mepolizumab. Although it needs to be interpreted with care, this comparison illustrates that the relative effects between the two treatments observed overall may not be carried forward across different sub-populations. This suggests that an indirect comparison based on

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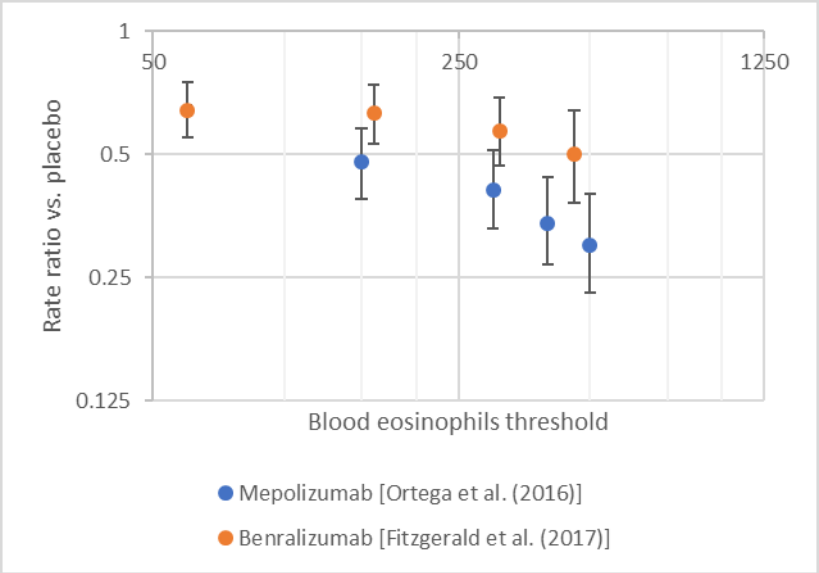
	subgroup analyses, such as that presented in Yancey et al., 2017 (which showed that the rate ratio of mepolizumab vs. placebo for exacerbations among patients with a history of >=3 exacerbations in the past year and eosinophils of >=300 cells/µL at baseline was 0.34 [95% CI 0.23, 0.51]) in the relevant sub-population for decision-making may be more appropriate than a matching adjusted indirect comparison in a wider population.  ○ Differences in effect modification seen by baseline eosinophils threshold may also exist by ACQ score or exacerbation history. However, there is currently insufficient information published to assess this. • On this basis, the underlying eosinophil treatment effect modifier may act to different extents for mepolizumab and benralizumab and therefore a matching-adjusted indirect comparison may no longer be a suitable method for an indirect comparison unless information on baseline characteristics within targeted populations are available. In the absence of this, a traditional indirect treatment comparison, such as using the Bucher method, may be more appropriate for comparing the efficacy of mepolizumab and benralizumab.
9	We agree with AZ's and ERG's conclusion that the matching adjusted indirect comparison attempted for benralizumab and mepolizumab populations on maintenance OCS (ZONDA and SIRIUS) must be interpreted with caution because of the differences in the study population, design and assessment of outcomes.
	Additional comments
10	The committee noted that benralizumab's convenience of administration is considered a 'step change' due to the 8-weekly dosing and therefore the need for patients to attend hospital less often for injections. We believe this is a short-term advantage. GSK would urge the committee to consider the transition of benralizumab and mepolizumab to patient self-administration over the next 12-18 months ** COMMERICAL IN CONFIDENCE INFORMATION REMOVED ** Taking learnings from other therapy areas where biologics given at home has become standard practice (e.g. Rheumatoid Arthritis), respiratory medicine is looking ahead to formats soon to be made available (NICE has recently confirmed that mepolizumab in auto-injector form will be reviewed through the Commissioning Support Programme). ** COMMERICAL IN CONFIDENCE INFORMATION REMOVED **

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England Specialised Respiratory Clinical Reference Group
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Name of commentator person completing form:	[redacted] Lead Commissioner

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1	NHS England note the input from the clinical experts regarding standard of care (SOC) for people who have had 3 or more exacerbations in the last year and view that statement as inaccurate. The Respiratory CRG clinical view is that reslizumab is now the SOC following the NICE HTA and at many severe asthma centres approximately 10-20% of anti-eosinophilic biologic prescribing is currently for reslizumab.
2	With regards to the statement from the clinical experts that 60% of people starting mepolizumab will be taking maintenance oral corticosteroids (OCS) the Respiratory CRG clinical view is that in their experience approximately 80% of people starting mepolizumab are on OCS. As this has a significant impact on the economic modelling NHS England would suggest obtaining the correct data. The UK severe asthma registry collects information on patients starting biologics and would be happy to provide this information.
3	Benralizumab is included in the 2018 iteration of Global Initiative for Asthma (GINA)
4	The Respiratory CRG clinical view is that there is no evidence to suggest that reslizumab is OCS sparing, which is suggested on page 3.
5	NHS England do support the development of products which can be self-administered as there is a significant burden on patients currently having to attend hospital services but would want to see this at a cost-effective price for the NHS.
6	NHS England note that NICE's assessment seems appropriate as the outcomes are the same as Mepolizumab and has no cost benefit.
7	The Respiratory CRG Patient and Public Voice member (Asthma UK) will be submitting their own organisational response.

Insert extra rows as needed

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Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by **5pm on Fiday 1 June 2018** on **email:** TACommA@nice.org.uk

`	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Teva UK Limited]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

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Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments by **5pm on Fiday 1 June 2018** on **email:** TACommA@nice.org.uk

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the following statement in the ACD is not accurate: ***'reslizumab is not frequently used in clinical practice because it is given intravenously, which is not convenient for patients.'*** Reslizumab received its approval from NICE (TA479) nine (9) months later than mepolizumab. Usage of reslizumab is currently lower than mepolizumab as it was only recently funded by NHSE, but is already in routine use by several of the Tertiary Asthma centres in England. We also disagree that reslizumab is not convenient for patients. Currently both anti-IL5 biologics are administered monthly only within a hospital setting and therefore patients have to travel each month irrespective of the treatment given although we do accept that the route of administration is different.
2	We disagree with the following statement: ***'However, the clinical experts noted that the intravenous injections are a disadvantage and limit its use. The committee concluded that for people who have had 3 exacerbations and are not taking oral corticosteroids, the most appropriate comparator in current NHS practice is standard care.'*** Reslizumab does not have limited used according to its route of administration and post NICE approval (TA479) and NHSE funding is being used routinely by numerous tertiary asthma centres and is therefore included in current NHS practise and should be an appropriate comparator.
3	We are concerned that with the following statement: ***'the company assumed that benralizumab and reslizumab have the same clinical efficacy.*** We agree with the following ERG statement: ***The ERG agreed that a MAIC comparing benralizumab with reslizumab is not feasible, but it noted that there is no evidence to support the assumption of clinical equivalence.'*** In addition we would like to draw to the committees attention a subgroup analysis from the reslizumab Phase III trial for patients with 3 or more CAEs that was presented at the European Respiratory Society (ERS) meeting last year which showed a difference compared to the subgroup analysis for benralizumab as quoted in the ACD for a similar patient population: Reslizumab: **67% (RR 0.33, 95% [0.22, 0.49])** published at the ERS 2017 Chauhan *et al.* compared to: Benralizumab **53% (RR 0.47, 95% [0.32 to 0.67])** as stated in the ACD

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Benralizumab for treating severe eosinophilic asthma [ID1129]

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Consultation on the appraisal consultation document – deadline for comments by **5pm on Fiday 1 June 2018** on **email:** TACommA@nice.org.uk

4	We are concerned that the following statement in the ACD is not accurate: ***'However, the committee noted that reslizumab is used much less frequently than mepolizumab in the NHS, and it considered that the comparison of benralizumab with reslizumab is not critical to its decision making.'*** Reslizumab only received its approval from NICE (TA479) in October which was nine (9) months later than mepolizumab. Usage of reslizumab will be lower than mepolizumab due to the later approval and was only recently funded by NHSE. Reslizumab is however already in routine use and therefore is critical to the decision making of the committee.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

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Additional Comments from Professor Tim Harrison on Benralizumab for severe asthma. 30.5.18

1. I believe the estimate for maintenance oral steroid use of 47% is too low. This figure is based on data from the BTS severe asthma register which includes all patients with severe asthma many of whom are less severe than the pool being considered for biological treatment. As discussed at the first meeting we have seen 66% of patients being considered for mepolizumab to be on maintenance prednisolone and discussions with other severe asthma centres suggests this to be a better estimate.

2. Although Meopolizumab is the main comparator for patients on maintenance prednisolone or 4 plus exacerbations, standard care is also appropriate for patients who prefer not to travel for many hours to receive a 4-weekly injection. These patients choose therefore to remain on standard care and this should be used as the comparator for these patients.

3. I can see no problem with having 4 plus exacerbations for one drug and 3 plus for another drug, we already have this for Resilizumab and it seems unlikely that all future biologics will fit under the same criteria in the hope of 'keeping it simple'.

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

Name	[redacted]
Role	Professor of allergy and pulmonology
Other role	NHS Professional
Organisation	Scottish Centre for Respiratory Research , Ninewells Hospital ,University of Dundee
Location	Scotland
Conflict	Yes
Notes	I have received payment from Astrazeneca for giving a postgraduate educational talk and attending an advisory board and have received support from Astrazeneca to attend the American Thoracic Society . These activities are unrelated to Benralizumab

Comments on the ACD:

I wish to express my concerns about the recent NICE benralizumab appraisal document [ID1129] which I read today.

From what I can see NICE have compared benralizumab to mepolizumab on top of standard of care (SOC) as ICS/LABA in severe eosinophilic asthma (SEA) patients who have 4 or more exacerbations in previous year .

In my clinical experience I would say approximately 5-10% of my patients with these criteria are actually receiving mepolizumab -ie SOC in most of my severe eosinophilic asthma patients in fact does not include Mepolizimab per se -which is therefore not SOC in the majority of patients .

I would also say that the data in terms of clinical benefit are very compelling for adding benralizumab on top of SOC (as ICS/LABA) in SEA patients who have 3 or more exacerbations .

Hence in my humble opinion it this is group of patients which should be used for the cost effectiveness analysis by NICE.

Benralizumab for severe asthma:

NICE STA

Addendum:

Between 1st and 2nd NICE Appraisal Committee meetings

Additional analyses conducted by the ERG assuming revised PAS prices for Benralizumab vs SOC

11th June 2018

Confidential information that is commercial-in-confidence is highlighted and underlined.

The revised PAS price for benralizumab is [redacted] per 30 mg subcutaneous injection.

Table 1 Derivation of PenTAG's base-case ICERs (£ per QALY)

	Item	PenTAG's base case	Company's base case	ICER for BEN+SOC vs SOC
1	Asthma-related mortality	Age-stratified probabilities for hospitalised patients of 65 years of age and older, and for patients of 45-100 years old requiring OCS and NR the probabilities are the same as in the CS; in all other age categories, they were assumed ~2.5 times lower than in the company's model.	See **Error! Reference source not found.**	£29,807
2	mOCS use at baseline	41.7% (Heaney et al., 2010) for SOC comparison, 60% for the MEPO comparison	54.1% for SOC comparison, 78.6% for the MEPO comparison	£29,996
3	Administration costs of biologics	Costed supervision after the admin of biologics; assumed the same admin time for MEPO and BEN.	Monitoring time not costed; administration of MEPO takes 5 mins longer than for BEN	£28,479
4	Treatment discontinuation rate	0.0041/cycle (average across the pivotal trials)	0.0048/cycle	£28,173
	ERG's base case: 1+2+3+4			**£32,179**
	Company's base case:			**£28,103**

The detailed results of the base-case pair-wise analysis are presented in the table below.

Table 2 ERG's base-case results with revised price vs. SOC

Technology	Total discounted costs (£)	Total discounted QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	**£32,179**

SoC	[redacted]	[redacted]	-	-	-

Scenario analyses

Similar to Section 5.2.2 in our original report, the ERG conducted the following scenario analyses with revised PAS price for benralizumab:

- Asthma-related mortality set to zero
- Using EQ-5D-5L health state utility values patient's age at the start of treatment
- Using results of a MAIC scenario analysis for exacerbation trials including MUSCA trial
- Proportion of patients responding to all treatments after 52 weeks set to 50% for both OCS and non-OCS users

Results are summarised in Table 3 below.

Table 3 Scenario analyses relative to the ERG's base case

Assumptions	ICER for BEN vs.
	SOC
Set asthma-related mortality to zero	£59,961
Use EQ-5D-5L utilities from the pivotal trials directly, rather than mapped values onto EQ-5D-3L	£35,237
PenTAG Base Case	**£32,179**
Patient's age at the start of treatment set to 44.9 (as in Heaney et al. (2010) [5])	£31,525
Using results of MAIC scenario analysis for exacerbation trials including MUSCA trial (MEPO comparison)	NA
Proportion of patients responding to all treatments after 52 weeks set to 50% for both OCS and non-OCS users	£31,429

Table 4 ERG's scenario analyses vs. SOC using revised PAS prices

Scenario	Total discounted costs (£)	Total discounted QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Patient's age at the start of treatment set to 44.9	[redacted]	[redacted]	[redacted]	[redacted]	£31,525
	[redacted]	[redacted]	[redacted]	[redacted]	-
					N/A

Using results of a MAIC scenario analysis for exacerbation trials including MUSCA trial (MEPO comparison)					
Proportion of patients responding to all treatments after 52 weeks set to 50% for both OCS and non-OCS users	[redacted]	[redacted]	[redacted]	[redacted]	£31,429
	[redacted]	[redacted]	[redacted]	[redacted]	-
Use EQ-5D-5L utilities directly, rather than mapped values onto EQ-5D-3L	[redacted]	[redacted]	[redacted]	[redacted]	£35,237
	[redacted]	[redacted]	[redacted]	[redacted]	-
Set asthma-related mortality to zero	[redacted]	[redacted]	[redacted]	[redacted]	£59,961
	[redacted]	[redacted]	[redacted]	[redacted]	-

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Benralizumab for treating severe asthma [ID1129]
Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Asthma UK and consequently I will not be submitting a personal statement.

Name: .....Olivia Allen.....

Signed: .....

Date: .....13/06/18.....