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
   - Association of Respiratory Nurse Specialists
   - British Thoracic Society (BTS)
   - GlaxoSmithKline UK Ltd
   - NHS England
   - Teva UK Limited

   **RCP endorse the response from BTS*
   **DHSC submitted a no comment response*

3. **Comments on the Appraisal Consultation Document from experts:**
   - Lehanne Sergison – patient expert nominated by Asthma UK
   - Dr Samantha Walker – patient expert nominated by Asthma UK

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

5. **ERG responses to comments on ACD2**

6. **ERG critique of company ACD2 response**

7. **Expert statement** from:
   - Dr Adel Mansur – clinical expert, nominated by AstraZeneca

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 (ACD2)

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 Social Care 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 document (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 and Social Care, 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.

No.	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Professional Group	British Thoracic Society	1. We are concerned that this recommendation may imply that the drug would only be considered second line to Mepolizumab, even if the drugs were equally cost effective, in the final approval. As Benralizumab appears to have greater efficacy, with trial evidence of impact on lung function and quality of life, over and above the reductions seen in exacerbations, then this would be a disadvantageous position. The practical advantage of eight weekly injections, will also have cost to the nation savings, even though this is not calculated completely in NICE assessment. **2. Has all of the relevant evidence been taken into account?** We are uncertain if the work by FitzGerald et al. Lancet Respir Med. 2018 Jan;6(1):51-64, has been considered – this specifically looks at predictors of enhanced response with benralizumab. **3. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Despite ZONDA, SIROCCO and CALIMA being accounted for, it still not clear why an eosinophil cut off of 400 cells/uL is chosen based on clinical evidence. Cost appears to be the only reason for this arbitrary number essentially displacing reslizumab therapy. This drug will already be poised as second line to mepolizumab based on the NICE recommendations. The 400cell/uL would discriminate against patients who reflect the trial populations may potentially lose out. We are also concerned about the timescale placed on eosinophil counts – from this draft guidance: - the blood eosinophil count has been recorded as 400 cells per microlitre or more in the past 12 months Many of the most patients who stand to benefit most from these treatments have eosinophil counts suppressed by oral steroids. Additional disadvantage will be set for patients who have originally been trialled on Mepolizumab, where there is clear evidence of the ability to suppress eosinophils but with some patients not gaining clinical benefit. We strongly believe the phrase should be at worst….eosinophilic in the last 12 months, or in the case of patients who have already received an unsuccessful trial of Mepolizumab…then were demonstrated to have eosinophils above 300 cell per microliter in the 12 months prior to their initial trial of Mepolizumab.	Thank you for your comments. The use of benralizumab in people who had tried mepolizumab has not been considered in this appraisal as these patients were not included in the trials. The recommendations for benralizumab are not the same as the trial inclusion criteria because it is only recommended when reslizumab is a treatment option where it is cost effective (recommended with a blood eosinophil count of 400) Furthermore, the date at which a high eosinophil count has to be recorded should not be specified and has been amended in the final publication.

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			4. **Are the recommendations sound and a suitable basis for guidance to the NHS?** No. We strongly disagree with the draft recommendation that benralizumab is recommended for a narrow population of people with blood eosinophils of 400 or more with at least 3 exacerbations in the last 12 months in whom mepolizumab is not an option. The summaries of clinical effectiveness used to generate this patient group suggested in the ACD are not reasonable interpretations of the evidence. We feel that the current provisional recommendations are not sound and are not a suitable basis for guidance to the NHS. 5. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Unknown.	The recommendations are reflective of all evidence and was considered carefully by the committee including frequency of dosing and ease of administration
2	Patient Group	Asthma UK	Severe asthma patients have a significant unmet need for more and better treatments. 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 200,000 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 a disproportionate number of the people that die from asthma have severe asthma (40% of those who died). The severe asthma patient group is one with a significant unmet need. Current oral corticosteroid (OCS) treatments often result in unpleasant side effects such as sleep disturbance and increased appetite and long-term co-morbidities such as diabetes and osteoporosis. As new Asthma UK research shows, there is significant disparity in referral criteria and rates for severe asthma, stopping many patients from accessing specialised care (Asthma UK, Slipping through the net, 2018, https://www.asthma.org.uk/get-involved/campaigns/publications/difficult-and-severe-asthma-report/). New monoclonal antibody treatments are welcomed, but are still difficult to access New monoclonal antibody treatments such as benralizumab offer a welcome alternative treatment option for those with severe asthma. However, referral rates to severe asthma centres and prescriptions for these new treatments are low and variable. This may be because non-steroid-based treatments for severe asthma are still relatively new and many healthcare professionals may not know if their patients could benefit from the new treatment options. Although existing biologics have offered relief of symptoms to some, they are limited in that they are only made available to a specific sub-population (e.g. people with eosinophil count of 400 and three or four exacerbations per year), and not all monoclonal antibody treatments work for each individual patient. As such, the approval of a new biologic offers an opportunity to help more people with severe asthma. On behalf of people with severe asthma, Asthma UK aims to improve access to specialised services and to make new treatments available to all who could benefit. Asthma UK would also like to see	Thank you for your comments.

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			further research into monoclonal antibodies to promote more targeted prescribing, improving patient outcomes and reducing the prescription of ineffective treatments. The eligibility criteria for benralizumab are too restrictive and may mean people miss out on life changing treatments 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 welcomes NICE's decision to approve its use on the NHS in England. However, Asthma UK is concerned that the guidance only approves the use of benralizumab for patients with an eosinophil count of over 400 and three exacerbations within the past year, even though there is evidence that benralizumab may be effective for a wider population. Patients with an eosinophil count of 300-399 and 3 exacerbations in 12 months are currently not eligible for other monoclonal antibodies available, and their only treatment option is OCS which cause significant adverse side effects. We are concerned that the restrictions on eligibility to benralizumab mean many people will continue to miss out on life changing treatments and remain on damaging OCS treatments indefinitely. As one severe asthma clinician told us in our recent report, these patients on long term OCS often miss out on specialised care and new treatments: The problem is long-term damage done by steroids by the time they get to us. Also, once they are stable on steroids, they kind of slip through the net, their hospital admissions reduce, so they're not flagged up as often.• As well as lowering the eosinophil threshold, Asthma UK would like to see continuous OCS use as another criterion for eligibility for benralizumab (and other monoclonal antibodies). Patients on OCS may appear ineligible for benralizumab because eosinophil levels are reduced by OCS and OCS also suppress asthma attacks. A lower eosinophil count does not necessarily mean that a patient''s asthma is less severe and they should still be eligible for benralizumab. The guidance is too restrictive over when benralizumab can be prescribed over another monoclonal antibody. Additionally, Asthma UK is concerned at the guidance's stipulation that for eligible patients, mepolizumab should be tried before benralizumab. It is not practical from a patient's perspective to switch from another biologic to benralizumab. In order to meet the eligibility criteria as specified in the draft guidance, there would have to be a significant period between treatments, and off any eosinophil-suppressing treatments, during which time the patient's asthma is at risk of deteriorating, putting them at serious and unacceptable risk of exacerbations. Benralizumab may be more favourable to a patient for reducing the burden of managing severe asthma, as it requires less frequent dosing and in the method of administration. This is particularly important in light of patients travelling long distances and taking time off work to visit specialist clinics. Patient choice and wellbeing should be an important factor in which monoclonal antibody should be prescribed by clinicians. In determining which monoclonal antibody to prescribe, suitability and preference for each patient should be considered, and the guidance should not promote one treatment over another. Recommendations from Asthma UK on the second appraisal of benralizumab for treating severe	The recommendations for benralizumab are not the same as the entry criteria for the trial because it is only recommended when reslizumab is a treatment option where it is cost effective (recommended with a blood eosinophil count of 400 and have had at least 3 exacerbations requiring oral corticosteroids who were not eligible for treatment with mepolizumab). People on maintenance oral corticosteroids (mOCS) OR 4 exacerbations are eligible for mepolizumab and benralizumab is not cost-effective compared with mepolizumab. Additionally benralizumab is not cost effective in people with eosinophil counts of 300-399 and 3 exacerbations who are not on mOCS. The trials did not compare oral corticosteroids with benralizumab so the cost effectiveness compared with continuous oral corticosteroids has not been assessed. Patients on continuous OCS are potentially eligible for mepolizumab. The use of benralizumab in people who had tried mepolizumab has not been considered in this appraisal as these patients were not included in the trials. Furthermore, the date at which a high eosinophil count has to be recorded should not be specified and has been amended in the final publication. The recommendations are reflective of all evidence and was considered carefully by the committee including frequency of dosing and ease of administration

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			eosinophilic asthma: • Asthma UK calls for NICE to approve benralizumab as a treatment for the wider population for whom it is clinically effective and for whom there are no alternative new treatments (patients with 300+ eosinophil count and at least three exacerbations in the past year) • Asthma UK calls for NICE to approve benralizumab as a treatment for patients with severe asthma who are already receiving continuous OCS treatment • Asthma UK calls for NICE to remove the requirement that mepolizumab should be tried before benralizumab • Asthma UK calls for NICE and AstraZeneca to reach agreements on price and cost effectiveness to extend eligibility of the treatment to the maximum number of potential patients who could benefit	
3	Professional Group	Association of Respiratory Nurse Specialists	1. We are concerned that the evidence that is available on benralizumab has not been applied within this guidance. 2. The two studies on benralizumab (SIROCCO and CALIMA) used an eosinophil count of 300 for study entry not 400 as NICE are recommending 3. The analysis from these studies demonstrated that patients with an eosinophil count of 300 or higher along with 3 exacerbations in the previous 12 months had a positive response. 4. We feel the criteria should include patients who have had 3 or more exacerbations within the previous 12 months OR those also on continuous oral steroids. 5. The eosinophil count for mepolizumab treatment is 300 and you suggest that people for benralizumab is 400. If someone is on mepolizumab it will invariably lower their eosinophil count. How can you then switch to benralizumab, does the patient have to have a break from treatment altogether and wait for their eosinophil count to rise to 400 before being allowed to have benralizumab? This surely would not be ethically or morally correct. 6. We would ask that NICE reconsider these guidelines based on the evidence currently available.	Thank you for your comments. The recommendations for benralizumab are not the same as the entry criteria for the trial because it is only recommended when reslizumab is a treatment option where it is cost effective (recommended with a blood eosinophil count of 400 and have had at least 3 exacerbations requiring oral corticosteroids who were not eligible for treatment with mepolizumab). People on maintenance oral corticosteroids (mOCS) OR 4 exacerbations are eligible for mepolizumab and benralizumab is not cost-effective compared with mepolizumab. The date at which a high eosinophil count has to be recorded should not be specified and has been amended in the final publication.
4	Professional Group	NHS England	1) We are concerned that the proposed treatment population is not clinically relevant for the following reasons: 1. The eosinophil count should be 300. Both phase III pivotals (SIROCCO and CALIMA) used an eosinophil count of 300 for study entry. 2. Pooled analysis of SIROCCO and CALIMA clearly demonstrates that people with eosinophils of 300 or higher and 3 exacerbations in the previous 12 months have an enhanced response (Fitzgerald et al. Lancet Respir Med 2018; 6: 51-64). 3. For people with severe asthma the ability to reduce/remove oral corticosteroids (OCS) is frequently as, or more, important than preventing future attacks. Given the strength of the ZONDA data, the population should include people with 3 or more exacerbations or who are taking continuous OCS. Otherwise it is illogical to have a clinically significant	Thank you for your comments. The recommendations for benralizumab are not the same as the entry criteria for the trial because it is only recommended when reslizumab is a treatment option where it is cost effective (recommended with a blood eosinophil count of 400 and have had at least 3 exacerbations requiring oral corticosteroids who were not eligible for treatment with mepolizumab). People on maintenance oral corticosteroids (mOCS) OR 4 exacerbations are eligible for mepolizumab and

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			reduction in OCS as one of the definitions of an adequate response at 12 months. OCS use also predicts response to benralizumab (Fitzgerald et al. Lancet Respir Med 2018; 6: 51-64). 4. There have been no clinical trials of benralizumab in people with severe eosinophilic asthma in whom 'mepolizumab is not a treatment option' or have failed a trial of mepolizumab. 2) We are concerned that the committee has misinterpreted the available clinical evidence to come to the conclusion that the 'mixed' population suggested by the company is not suitable for considering the cost effectiveness of benralizumab compared with standard care for the following reasons: 1. This mixed population equates to the mepolizumab and omalizumab HTAs, neither of these HTA are based on trial data suggesting that this is the correct target population. There is stronger evidence that this is the correct population for benralizumab based on the published responder analysis (Fitzgerald et al. Lancet Respir Med 2018; 6: 51-64). 2. The committee are incorrect in their assumption that the company's proposed population include people with different severities of asthma. The whole population falls within the ERS/ATS definition of severe asthma (Chung et al. Eur Respir J 2014; 43: 343-73) and as clinicians we would not differentiate between individual people with severe asthma in the way suggested by the committee. 3. Eosinophil level does not differentiate between asthma severity, the level in an individual person varies significantly in time and with treatment (Newby et al. Plos One 2014). People with mild asthma can have elevated blood eosinophil levels. 3) Should the eosinophil trigger level be standardised for all IL5 inhibitors? 4) There is no logic to the failed mepolizumab threshold. They are alternative drugs.	benralizumab is not cost-effective compared with mepolizumab. As benralizumab is the 3rd to market product, it needs to be compared against comparators specified in scope. The benralizumab recommendations specified eosinophil count, number of exacerbations and OCS use in order to make clear how it compares with the recommendations for existing biologics mepolizumab and reslizumab).This is written to show where it is recommended in the current treatment pathway. In addition, eosinophil count was an inclusion criterion for the main trial and is not used as the sole indicator of asthma severity. Eosinophil count is however of relevance when this is an anti-eosinophil agent. Expanding the recommendation to a currently biologic ineligible population was carefully considered, but the evidence is limited and it is not cost effective. Entry trial data for all 3 biological treatments (benralizumab, mepolizumab and reslizumab) were different which makes any form of standardisation difficult. Benralizumab is recommended only as an alternative to reslizumab, where it is cost-effective. Benralizumab is not cost-effective compared with mepolizumab, and it is agreed they are alternative drugs.
5	Comme	Patient	I am concerned that the recommendation will mean that a large number of patients will not meet the criteria of having an eosinophil level over 400. Patients with severe eosinophilia asthma are	Thank you for your comments.

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	ntator	expert	desperate to lead as full and meaningful lives as possible without the burden the disease and taking OCS. The research has proven that potentially Benralizumab could have life changing benefits to patients with eosinophil levels of 300 and to deny them this opportunity seems most unjust. I am aware of a number of patients who have been treated with Mepolizumab and have had to stop their treatment because of adverse effects or no improvement. Some of these patients do not meet the criteria of Reslizumab and will not meet the guidance for Benralizumab. From a patient's perspective, it seems most unreasonable that despite the research demonstrating that Benralizumab can make significant improvements to patients with an eosinophil level of over 300 NICE has made a recommendation that will deny this group of patients access to a potentially life changing treatment. In making their recommendation, I am concerned that the panel has not put sufficient weight on the benefit of administering Benralizumab every eight weeks as opposed to four weekly with Mepolizumab, and more importantly the added benefit that it may be self- administered. This is a huge benefit to patients. Many patient have to travel long distances to specialist centres for Mepolizumab or Reslizumab and may have to take a day off work, arrange child care etc and there is also the financial cost to consider. Patients with chronic condition are constantly fearful of losing their jobs due to a poor sickness records and taking time off work for appointments etc. Furthermore, the impact of long term ocs use many of these patients may have co-morbidities and potentially may be under the care of a number of hospital consultants thereby juggling lots of hospital appointments. Self - administration of be Benralizumab would be huge step forward for patients and would surely free up a significant amount of time in specialist centres. The recommendation does not give any consideration to patients who are on permanent ocs to manage their condition who may not have asthma exacerbation as such but may benefit from Benralizumab. Prednisolone is dreadful drug to take, which can cause a multitude of side effects, Benralizumab is potentially steroid sparing and should be considered as an option for these patients.	The recommendations for benralizumab are not the same as the entry criteria for the trial because it is only recommended when reslizumab is a treatment option where it is cost effective (recommended with a blood eosinophil count of 400 and have had at least 3 exacerbations requiring oral corticosteroids who were not eligible for treatment with mepolizumab). People on maintenance oral corticosteroids (mOCS) OR 4 exacerbations are eligible for mepolizumab and benralizumab is not cost-effective compared with mepolizumab. The recommendations are reflective of all evidence and was considered carefully by the committee including frequency of dosing and ease of administration There has been no comparison of benralizumab with mOCS and this evidence was not considered by the committee in this appraisal.
6	Commentator	Professor of allergy and pulmonology- Scottish Centre for Respiratory Research	I feel the NICE guidance will be detrimental to my patients with severe eosinophlic asthma if as suggested I have to first show that they fail on mepolizumab as standard of care. Aside from any cost issues I feel it is important to have to the option of different biologics even within the same class ,bearing in mind that benralizumab works via a different receptor mediated mechanism of depleting eosinophils .At present our response rate to Mepolizumab as unit is running at around 30% in highly selected patients who have been evaluated in an MDT setting .Hence having only one default anti-IL5 is surely going to have an adverse impact on patient care .Moreover I don't see the logic in setting a blood eosinophil cut off of 400/ul along with an exacerbation history of at least 4 in the past year as this will markedly limit the number of eligable patients who could recieve benralizumab . All of this along with a more patient friendly dosing regimen every 8 weeks for benralizumab (after the first 3 doses) would mean my patients would be missing out of an alternative highly effective option. Bear in mind by the time patients have failed on Mepolizumab they are then a further 12 months down the line and have been exposed to the cumulative systemic adverse effect burden of another 4-8 weeks of oral corticosteroid . As someone who has been exposed to oral corticosteroids as a patient I find this	Thank you for your comments. The use of benralizumab in people who had tried mepolizumab has not been considered in this appraisal as these patients were not included in the trials. The recommendations for benralizumab are not the same as the entry criteria for the trial because it is only recommended when reslizumab is a treatment option where it is cost effective (recommended with a blood eosinophil count of 400 and have had at least 3 exacerbations requiring oral corticosteroids who were not eligible for treatment with mepolizumab). People on

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			unacceptable.	maintenance oral corticosteroids (mOCS) OR 4 exacerbations are eligible for mepolizumab and benralizumab is not cost-effective compared with mepolizumab.
7	Commentator	Consultant Respiratory Physician - UK Severe Asthma Network	1. <u>General</u> As clinicians looking after people with severe asthma in the UK, we would like to comment on the NICE appraisal consultation document on Benralizumab for treating severe eosinophilic asthma. We are pleased that multiple novel therapies have been proven to be both clinically and cost effective and for some people with severe asthma these options have been transformative. However, there is a clear need for additional therapeutic options. We strongly disagree with the draft recommendation that benralizumab is recommended for a narrow population of people with blood eosinophils of 400 or more with at least 3 exacerbations in the last 12 months in whom mepolizumab is not an option. The summaries of clinical effectiveness used to generate this patient group suggested in the ACD are not reasonable interpretations of the evidence. We feel that the current provisional recommendations are not sound and are not a suitable basis for guidance to the NHS. As the clinical leads for severe asthma care across England we do not think that the committee has correctly interpreted the evidence to produce a logical summary of the clinical effectiveness. We strongly support the company's proposed population from a clinical perspective and urge NICE and Astra Zeneca to have further discussions with regards the Patient Access Scheme to allow clinicians to treat the correct patient cohort and people with severe asthma to receive the care that they need. The following consultant respiratory physicians have been involved in producing this document and endorse its findings: Dr Andrew Menzies-Gow, Royal Brompton Hospital. Professor Ian Pavord, University of Oxford Dr Dave Allen, Wythenshawe Hospital Dr Adel Mansur, Birmingham Heartlands Hospital Professor Salman Siddiqui, Glenfield Hospital Professor Dominick Shaw, Nottingham University Hospitals NHS Trust Dr David Jackson, Kingâ's Health Partners Dr Paul Pfeffer, Bartâ's Healthcare Dr Robin Gore, Addenbrookes Hospital Professor Anoop Chauhan, Portsmouth Hospital Professor Ian Sabroe, University of Sheffield Dr Ian Clifton, Leeds Teaching Hospital NHS Trust Dr Matthew Masoli, Derriford Hospital Dr Paddy Dennison, Southampton University Hospital	Thank you for your comments. The recommendations for benralizumab are not the

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			2. Section 1.1 Proposed Treatment population This population is not clinically relevant and has been produced due to a fundamental lack of understanding of severe eosinophilic asthma. As the clinical leads for severe asthma at nationally commissioned centres we agree with the company's proposed population for the following reasons: 1. The eosinophil count should be 300. Both phase III pivotals (SIROCCO and CALIMA) used an eosinophil count of 300 for study entry. 2. Pooled analysis of SIROCCO and CALIMA clearly demonstrates that people with eosinophils of 300 or higher and 3 exacerbations in the previous 12 months have an enhanced response (Fitzgerald et al. Lancet Respir Med 2018; 6: 51-64). 3. For people with severe asthma the ability to reduce/remove oral corticosteroids (OCS) is frequently as, or more, important than preventing future attacks. Given the strength of the ZONDA data, the population should include people with 3 or more exacerbations or who are taking continuous OCS. Otherwise it is illogical to have a clinically significant reduction in OCS as one of the definitions of an adequate response at 12 months. OCS use also predicts response to benralizumab (Fitzgerald et al. Lancet Respir Med 2018; 6: 51-64). 4. There have been no clinical trials of benralizumab in people with severe eosinophilic asthma in whom mepolizumab is not a treatment option or have failed a trial of mepolizumab. 5. As clinicians we do not understand what is meant by 'mepolizumab is not a treatment option'? The HTA for mepolizumab suggests treating for 12 months, it will be impossible to switch to benralizumab at that point as there is a requirement for an eosinophil count of 400 or higher in the last 12 months and in all cases mepolizumab will have suppressed the eosinophil count over that time period and potentially for several months following cessation of mepolizumab (Haldar et al. J Allergy Clin Immunol 2014; 133: 921-3). Are the committee suggesting that following an unsuccessful trial of mepolizumab people with severe asthma should have to continue with OCS and all their concomitant side effects until the eosinophil count recovers? 3. Pages 4-5 Why the committee made these recommendations We fundamentally disagree with the statement that the mixed population suggested by the company is not suitable for considering the cost effectiveness of benralizumab compared with standard care for the following reasons: 1. This mixed population equates to the mepolizumab and omalizumab HTAs, neither of these HTA are based on trial data suggesting that this is the correct target population. There is stronger evidence that this is the correct population for benralizumab based on the published responder analysis (Fitzgerald et al. Lancet Respir Med 2018; 6: 51-64). 2. The committee are incorrect in their assumption that the company's proposed population includes people with different severities of asthma. The whole population falls within the ERS/ATS definition of severe asthma (Chung et al. Eur Respir J 2014; 43: 343-73) and as clinicians we would not differentiate between individual people with severe asthma in the way suggested by the committee. 3. Eosinophil level does not differentiate between asthma severity, the level in an individual	same as the entry criteria for the trial because it is only recommended when reslizumab is a treatment option where it is cost effective (recommended with a blood eosinophil count of 400 and have had at least 3 exacerbations requiring oral corticosteroids who were not eligible for treatment with mepolizumab. People on maintenance oral corticosteroids (mOCS) OR 4 exacerbations are eligible for mepolizumab and benralizumab is not cost-effective compared with mepolizumab. Additionally benralizumab is not cost effective in people with eosinophil counts of 300-399 and 3 exacerbations who are not on mOCS. The use of benralizumab in people who had tried mepolizumab has not been considered in this appraisal as these patients were not included in the trials. It has not been recommended in people who have received mepolizumab. Benralizumab has not been recommended in people who would be eligible for treatment with mepolizumab because it is not cost effective compared with mepolizumab. Furthermore, the date at which a high eosinophil count has to be recorded should not be specified and has been amended in the final publication. As benralizumab is the 3rd to market product, it needs to be compared against comparators specified in scope. The benralizumab recommendations specified eosinophil count, number of exacerbations and OCS use in order to make clear how it compares with the recommendations for existing biologics mepolizumab and reslizumab) This is written to show where it is recommended in the current treatment pathway. In addition, eosinophil count was an inclusion criterion for the main trial and is not used as the sole indicator of asthma severity. Eosinophil count is relevant as benralizumab acts by reducing eosinophils

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			person varies significantly over time and with treatment (Newby et al. Plos One 2014). People with mild asthma can have elevated blood eosinophil levels. 4. Section 3.3 3.3 Please update to the GINA 2018 guidelines, which include benralizumab as a treatment option.	
8	Comparator company	Teva	We are concerned that with the following statement in section 3.13: 'It considered that although the simple assumption of clinical equivalence between the 2 treatments {benralizumab and reslizumab} is questionable, it is reasonable to assume that they are not very different.' We are not aware of any clinical data directly comparing these two treatments and therefore this assumption is unfounded. In addition we would like to draw to the committee's attention to indirect evidence that indicates a efficacy difference between these 2 treatments: subgroup analysis from the Phase III trials for patients with 3 or more CAEs: 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	Thank you for your comments. The committee's considerations about the efficacy of reslizumab compared with benralizumab are outlined in the FAD, taking into account the information provided (see section 3.9 of the FAD).
9	Comparator company	GSK UK	1. We believe the proposed population on which a draft positive recommendation has been issued for benralizumab represents a balanced reflection of the evidence presented throughout the appraisal process to date.The proposed population seeks to reflect where benralizumab has demonstrated value to the NHS and severe asthma patients relative to current NICE guidance in place for reslizumab and mepolizumab. The following comments highlight our ongoing concerns regarding: • The specificity of the proposed NICE guidance wording and possible consequences of its future implementation in practice • The conclusions drawn on the application of the comparative effectiveness of benralizumab versus mepolizumab • Limited additive benefit offered by benralizumab over current NICE recommended anti-IL5's **2. The description of the proposed NICE benralizumab guidance needs to be defined further to ensure its *appropriate* usage in clinical practice – 'where mepolizumab is not a treatment option'**	Thank you for your comments. After considering the comments received in response to the ACD2, the wording of the recommendations for benralizumab has been changed to make the specific

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			The current draft guidance wording stipulates '*and mepolizumab is not a treatment option*'. We strongly request that this wording is re-considered by the Committee and altered to '*and where an individual is ineligible for mepolizumab based on clinical criteria or has previously not adequately responded to mepolizumab'*. As the Committee is aware, NHS England directly commissions the Specialised Respiratory Services for Severe Asthma (adults) including the delivery of biologic therapy. One of the key roles of the specialist centres is to improve outcomes for people with severe asthma and to act as clinical gatekeepers to ensure appropriate access to high cost technologies (including biological agents), to prevent inappropriate use, unnecessary risk to patients and cost-effective use of resources to the NHS. Currently, to access a NICE recommended biologic therapy, a form (via the Blueteq system) must be completed. This sets out the NICE guidance criteria and we understand this is a series of tick boxes. We believe the implementation of the draft guidance wording '*and mepolizumab is not a treatment option*' via the Blueteq system is ambiguous for implementation and may be open to interpretation by clinicians, beyond the clinical and cost-effectiveness evidence appraised by NICE. This may subsequently lead to an unanticipated larger population likely to receive benralizumab than that defined in the final NICE guidance, inclusive of patient subgroups not shown to be cost-effective. A further consequence of this, is an increase in the overall budget impact which the specialised service is set up to gate keep. We recognise the need expressed by patients and clinicians for further treatment options for severe eosinophilic asthma, however we are concerned that the current draft guidance wording could indicate acceptance for benralizumab to be prescribed earlier in the treatment pathway and ahead of mepolizumab unless the draft guidance wording clearly states '*and where an individual is ineligible for mepolizumab based on clinical criteria or has previously not adequately responded to mepolizumab'.* Throughout the appraisal process the Committee has been clear in their conclusions - benralizumab has not demonstrated a cost-effective proposition compared with mepolizumab. This is owed to highly uncertain comparative efficacy derived through a matching adjusted indirect comparison as well as greater overall cost savings offered by the mepolizumab patient access scheme. We want to ensure that any future guidance recommendations for benralizumab clearly reflects the appraisal of the evidence presented to support its later fair application within the NHS. **3. The description of the proposed NICE benralizumab guidance needs to be defined further to ensure its *appropriate* usage in clinical practice - *'at least 3 exacerbations in the past 12 months'*** The current draft guidance recommendation for benralizumab states:	populations that benralizumab is or isn't recommended for as clear as possible (see section 1 of the FAD) The recommendations have been updated to include the suggested changes (see section 1 of the FAD) Comments noted

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			'The person ……has had at least 3 asthma exacerbations in the past 12 months' We believe the Committee need to be aware of the possible implications in clinical practice if the current draft guidance wording remains in place. Based on the evidence appraised, we agree with the Committee's proposed population given the conclusions of the Committee in ACD2. We agree that in patients: • Blood eosinophil count ≥300 cells/μL, ≥3 exacerbations, not on maintenance oral corticosteroids – conclusion cannot be drawn as the ICER has not been presented • Blood eosinophil count ≥400 cells/μL, ≥3 exacerbations, not on maintenance oral corticosteroids – benralizumab is cost-effective compared with reslizumab and standard of care • Blood eosinophil count ≥300 cells/μL, ≥4 exacerbations, and / or on maintenance oral corticosteroids – benralizumab is not cost-effective compared with mepolizumab The future guidance recommendation will be used to develop the criteria captured via the Blueteq system for biologic access in tertiary care centres. Whilst we understand that NICE do not have a role in the development of future Blueteq criteria, further detail in the final guidance wording may help to address any ambiguity in clinical practice. Our suggested way to avoid the ambiguity is as follows: *'The person has agreed to and followed the optimised standard treatment plan, and* ***either:*** • *has had 3 asthma exacerbations needing systemic corticosteroids in the past 12 months or* • *at least 4 asthma exacerbations needing systemic corticosteroids and is ineligible for mepolizumab based on clinical criteria (or has previously not adequately responded to mepolizumab)'* **4. The description of the proposed NICE benralizumab guidance needs to be defined further to ensure its *appropriate* usage in clinical practice – 'severe asthma exacerbations'** We seek clarification on the apparent change to the draft guidance wording stated in ACD2 compared with that communicated to registered consultees and commentators on 26 June 2018 following the second Appraisal Committee Meeting. This is with respect to defining asthma exacerbations. The communication sent to registered consultees and commentators stated *'……the person has had 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months….*'. Whereas the draft guidance wording in ACD2 states '……*has had at least 3 asthma exacerbations in the past 12 months…*' The draft guidance wording could suggest that milder exacerbations (e.g. a worsening of symptoms without the need for treatment intervention) is credible criterium for consideration of benralizumab	The date at which a high eosinophil count has to be recorded should not be specified and the recommendations have been updated (see section 1 of the FAD)

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			therapy. To align to the definition of an exacerbation in the benralizumab pivotal trials, CALIMA and SIROCCO, the assumptions the manufacturer has included within their cost-effectiveness modelling, and to ensure consistency of NICE guidance for all biologics in severe asthma, we believe this wording should be altered to: '….has had at least 3 severe asthma exacerbations *needing systemic corticosteroids in the past 12 months…'.* We believe the consistency is important for the local implementation of guidance for clinicians and patients. **5. We agree with the Committee's conclusion that the method used to estimate the comparative effectiveness of benralizumab versus mepolizumab is not robust.** We agree with the Committee's conclusions with regards to the method of deriving and the presented results of the comparative effectiveness versus mepolizumab: • The rationale for the Matching Adjusted Indirect Comparison instead of a network meta-analysis of mepolizumab and reslizumab was not adequately justified • There remains uncertainty about the clinical effectiveness of benralizumab compared with mepolizumab (see comment 6). We shared our concerns in detail with respect to these points in addition to the overall conduct of the Matching Adjusted Indirect Comparison in the consultation to ACD1. *6.* **We continue to strongly disagree that the relative efficacy between benralizumab and mepolizumab in the intention to treat populations can be applied to more severe sub-groups and believe this is supported by available published evidence for both mepolizumab and benralizumab.** The Committee stated that they heard from the manufacturer that the Matching Adjusted Indirect Comparison matched benralizumab patients to those in the mepolizumab trial and assumed that the relative difference in efficacy between the two treatments to be the same in the most severe subgroup as in the intention to treat population. As per our response to ACD1, we continue to strongly disagree that the relative efficacy between the two treatments in the intention to treat population can be applied to the most severe sub-populations and believe the published evidence for both treatments supports our disagreement. 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)	The committee noted that the evidence comparing the relative efficacy between benralizumab and mepolizumab is highly uncertain also considered that the rationale is inconsistent with the company's use of the clinical-effectiveness estimates from the MAIC (see section 3.9 of the FAD) Comments noted

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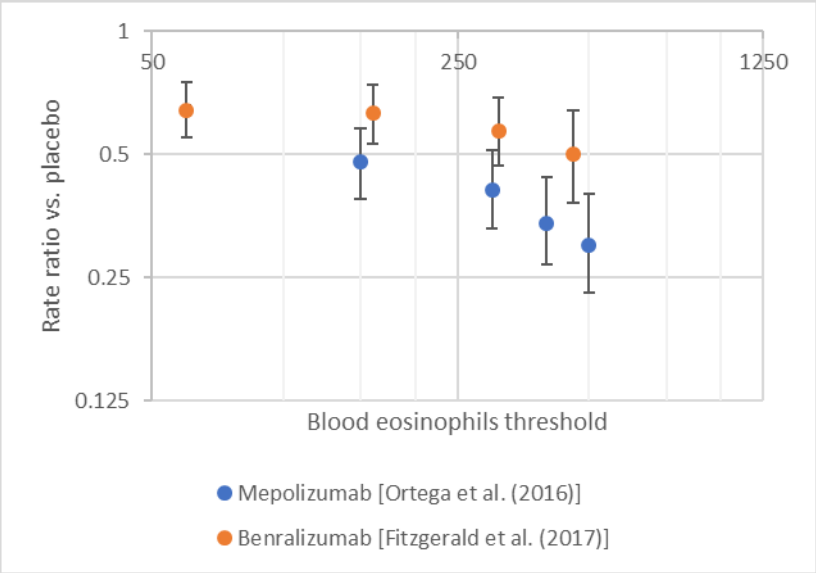
			▪ ≥ EOS 300 cells/μL is 0.41 (95% CI 0.33-0.51) ▪ ≥ EOS 400 cells/μL is 0.34 (95% CI 0.27-0.44) ▪ ≥ EOS 500 cells/μL is 0.30 (95% CI 0.23-0.40). The strength of this finding for mepolizumab is in contrast to that reported in the meta-analysis of the benralizumab studies (Fitzgerald et al., 2018). The 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 effect estimates for mepolizumab (Ortega et al. 2016) and benralizumab (Fitzgerald et al., 2017) are presented below.  With increasing eosinophil 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. Further, we refer the Committee to the EMA Preliminary Assessment Report for benralizumab,	

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			specifically to section 3.7.2 Balance of benefits and risks: *"Despite its dramatic effect on blood eosinophils benralizumab has demonstrated a modest effect on the frequency of exacerbations as reflected in relative terms by a ~40% reduction in the annual exacerbation rate and in absolute terms by a difference of about 0.5/year from 1.14 to 0.66/year. It is noteworthy that in similar patient populations, the two other anti-IL-5 agents (mepolizumab and reslizumab) achieved reductions in asthma exacerbations rates greater than 50% from a level of ~1.80/year."* Source: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004433/WC500245333.pdf. Available online: [Accessed 24 July 2018] *7.* **We agree with the NICE Committee, mepolizumab remains the relevant comparator for consideration in the mepolizumab NICE recommended population** We strongly agree with the Committee that mepolizumab and reslizumab are both the relevant comparators in this appraisal. However, we disagree that the uptake of mepolizumab should be considered low or lower than expected in the NICE mepolizumab population. The total population eligible for mepolizumab reflects *all* eligible patients irrespective of where they currently reside in the healthcare system; primary, secondary or tertiary care. The tertiary centres gatekeep access to mepolizumab and therefore the apparent uptake of mepolizumab may appear low as a percentage of all possible eligible patients. However, uptake of mepolizumab as a percentage of those patients eligible *and* referred to tertiary centres is higher. Further, as confirmed by the clinical expert on the committee, many severe asthma centres are still working through waiting lists of appropriate patients for mepolizumab.Therefore, we strongly agree with the Committee that in the NICE mepolizumab population, mepolizumab remains the key comparator for benralizumab. 8. **We believe the innovation offered by benralizumab will be of limited additive value for decision making purposes** *a) The benefit of dosing convenience offered by benralizumab is potentially short-lived* The Committee concluded that the dosing schedule for benralizumab would be beneficial for patients despite this not being captured within the cost-effectiveness analysis. GSK agrees with the Committee that reducing visits to hospital could be important for people with severe eosinophilic asthma. It is with the aim of reducing the burden of travel to hospitals for patients that **COMMERICAL IN CONFIDENCE INFORMATION REMOVED** *b) Long-term efficacy and safety of new therapies is of importance to patients choosing to commence biologic therapy – mepolizumab has substantial real-world evidence supporting its usage in practice.*	The committee's considerations about meoplizumab and reslizumab being relevant comparators and the deliberations around the uptake of biologic treatment are outlined in the FAD. The committee's considerations are outlined in sections 3.3 and 3.4 of the FAD. The committee's considerations about the innovation of benralizumab are outlined in the FAD. The committee's considerations are outlined in sections 3.2, 3.17 and 3.18 of the FAD.

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			As part of the treatment decision between a patient and their clinician there are many factors that need to be considered together and not in isolation. The Committee heard that some patients prefer not to receive biologic therapy because there is no long-term evidence on their use. We would like to remind the Committee that relative to reslizumab and benralizumab, the mepolizumab COSMOS and COLUMBA open-label extension studies have demonstrated that the safety and efficacy of mepolizumab was maintained for 1.5 years and 4.5 years respectively; with exacerbation reduction maintained and a safety profile reflective of earlier trials. This is in addition to the 15 months in which mepolizumab has been made available by the NHS. In this time patients have had the opportunity to take part in the REALITI-A registry study, which will generate real world evidence on mepolizumab outcomes and safety. Further the EMA's CHMP has recently recommended the use of mepolizumab in severe eosinophilic asthma paediatric and adolescent patients (≥ 6yrs - <18 years). *c) Dosing convenience is not a major reason why people with severe eosinophilic asthma, eligible for anti-IL5 treatment, choose not to take existing NICE recommended biologics.* The Committee heard that some people who meet the eligibility criteria for mepolizumab and reslizumab chose to remain on standard of care because of personal preferences and that the convenience of administration offered by benralizumab is potentially very beneficial to patients. Although somewhat limited by sample size, we would like to attempt to put this in context following a recent GSK-market research study. **COMMERICAL IN CONFIDENCE INFORMATION REMOVED**** **9. The manufacturer has not presented clinical and cost-effectiveness evidence to support a broadening of the proposed draft guidance population.** As we have already stated we believe the proposed population on which NICE has issued a draft positive recommendation for benralizumab is a fair reflection of the evidence presented and the appraisal process to date. Benralizumab remains not cost-effective in terms of acceptable ICER thresholds, compared with mepolizumab in the mepolizumab NICE recommended population. The comparison of efficacy is based on a highly uncertain Matching Adjusted Indirect Comparison and we presume that benralizumab has a higher net price compared with mepolizumab. In a scenario where further evidence and / or a revised PAS is provided by the manufacturer, and the final guidance population is broadened to the manufacturer's preferred population (blood eosinophil count of ≥ 300 cells/μL, ≥ 3 exacerbations in the previous 12 months and or on maintenance oral corticosteroids), we seek assurance that the ICER for the sub-population of blood eosinophil count of ≥ 300 cells/μL, ≥3 exacerbations and not on maintenance oral corticosteroids is presented for transparency. To date the ERG have concluded that the ICER is unlikely to fall within acceptable thresholds Further, based on the manufacturer's response to ACD1, observational epidemiology data	The committee's considerations about the clinical and cost-effectiveness evidence to support a broadening of the proposed draft guidance population are outlined in the FAD. The committee's considerations are outlined in sections 3.5-3.9 and 3.13 of the FAD.

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			suggested this population was also larger compared with that included in the benralizumab pivotal trials which therefore calls into question the generalisability of the trials. We have significant concerns that agreeing to a broader population would undermine the value for mepolizumab that GSK has offered to the NHS and patients in England and Wales. In this scenario, we would like to highlight our strong intention to seek a re-appraisal. We strongly refute that the differences in the comparative efficacy seen in the intention to treat populations can and should be applied to more severe sub-groups. Further, the rate ratio of mepolizumab vs. placebo for reduction in exacerbations among patients with blood eosinophils of ≥300 cells/μL at baseline and a history of ≥3 exacerbations in the past year 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). We also believe the economic proposition for mepolizumab would remain strong for the NHS in the case of a re-appraisal.	
10	Company	AstraZeneca	Dear Appraisal Committee Members, AstraZeneca welcomes the opportunity to comment on this ACD, and kindly asks the committee to consider the following key points: **1.** AstraZeneca has **revised the Patient Access Scheme (PAS)** to reduce the price of benralizumab to £[redacted] per vial (previously £[redacted] with the objective of being cost effective vs mepolizumab confidential net price. **2.** AstraZeneca is seeking a recommendation for a sub-group of the licensed patient population who will benefit the most from benralizumab, as per trial results. This requested population is the **same population as initially submitted** and is defined as follows: 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. For clarity, we will refer to this population in this document as the "base case population". Data from the registration studies shows increased benefit for the base-case population vs the ITT population: exacerbation reductions of 53% 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. **3.** With the revised PAS, the cost-effectiveness results are as follows: • **The ICER vs SOC in the base-case population where a recommendation is sought**	Thank you for your comments. Comments noted

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			is £25,192. We consider the ICER in this population vs SOC to be the basis for decision making, because SOC is a relevant comparator for the entire "base case population", and therefore it is not appropriate to divide this population into sub-groups for the comparison vs SOC (see detailed rationale in the technical response later in this document). • In the mepolizumab NICE recommended population, benralizumab is dominant versus mepolizumab (benralizumab net price vs mepolizumab **list** price) • In the reslizumab NICE recommended population, benralizumab is dominant versus reslizumab (benralizumab net price vs reslizumab **list** price) • As requested by NICE, we have calculated the ICER vs SOC in the current "non-biologic eligible" segment of the base-case population (300-399 EOS; AND exactly 3 exacerbations in prior year), which is £38,304. As described in the technical response, we believe that the primary ICER for decision making should be the ICER for the entire mixed, base-case population because: **a)** SOC is a comparator for the entire base-case population, **b)** The cost-effectiveness results are generalisable to real-world clinical practice in the NHS in England; and **c)** There is past precedent for using a mixed-population approach for decision making in the mepolizumab and reslizumab appraisals. **4.** **There is strong clinical support for final NICE guidance to be issued for benralizumab in a broader population than the current ACD proposal,** and clinical opinion that prescribing of mepolizumab and benralizumab (in suitable patients according to NICE guidance criteria) should be open to prescriber choice. Of 20 clinical experts who shared their views on the ACD with AstraZeneca on these specific topics and gave consent to be included in this response[1], 20 stated the need for benralizumab NICE guidance in a broader population than that proposed by the ACD, and 20 stated that prescribing of mepolizumab and benralizumab (according to NICE guidance criteria) should be open to prescriber choice (i.e. No pre-defined sequencing). **5.** Benralizumab provides **significant benefits** to patients and their families/carers compared	Benralizumab is only recommended when reslizumab is a treatment option where it is cost effective (recommended with a blood eosinophil count of 400 and have had at least 3 exacerbations requiring oral corticosteroids who were not eligible for treatment with mepolizumab). People on maintenance oral corticosteroids (mOCS) OR 4 exacerbations are eligible for mepolizumab and benralizumab is not cost-effective compared with mepolizumab. Additionally benralizumab is not cost effective in people with eosinophil counts of 300-399 and 3 exacerbations who are not on mOCS.

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			with mepolizumab and reslizumab: • 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 requires **less frequent dosing**, which could have a significant impact on patients' adherence to treatment, their quality of life, and on their families/carers. Benralizumab is administered every 8 weeks (after the first 3 doses which are administered every 4 weeks), compared with mepolizumab and reslizumab, which are administered every 4 weeks. Clinicians at the first appraisal committee meeting mentioned that benralizumab therefore meets a specific unmet need in the patient population who prefer to receive biologic treatment less frequently. • [redacted]	The recommendations are reflective of all evidence provided and was considered carefully by the committee including frequency of dosing and ease of administration
			6. Benralizumab will provide **productivity benefits** compared with mepolizumab and reslizumab, for patients receiving their biologic in the clinic. Productivity benefits have not been included in the cost effectiveness analysis, and are provided here as additional information, which the committee may wish to consider. Patients may require time off work to travel to and from the severe asthma clinic to receive a biologic. If we assume that on average a patient would require a half day (4 hours) off work to travel to and from the clinic, a patient on mepolizumab would require 52 hours (4*13 doses) off work each year compared with 26 hours off work (4*6.5 doses) each year for a patient on benralizumab (from year 2 onwards). Using the average earnings in the UK and having accounted for discontinuation and discounting, this means that for a working patient on benralizumab there is a productivity benefit of £1,684 on average over the lifetime compared with a working patient on mepolizumab (using a retirement age of 66). If we assume 50% of severe, eosinophilic asthma patients are working, this equates to a productivity benefit per benralizumab patient of £842 over the lifetime compared with a patient receiving	Productivity costs are not included in either the reference-case or non-reference-case analyses and therefore cannot be considered by the committee.

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			mepolizumab. [redacted]	Comments noted
			Based on the above points and the technical information below, we ask the committee to grant a recommendation for benralizumab in the base case 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 all of these patients have access to the specific benefits of benralizumab.	Comment noted – see above
11	Company	AstraZeneca	**Appropriateness of the mixed population to decision making** The ACD for benralizumab for the treatment of severe asthma states that "The mixed population compared with standard care is not appropriate for the purposes of decision making" for the following reasons: 1. Standard of care is not the only comparator in this population 2. There is major doubt about the generalisability to the NHS in England Below we seek to address these points as well as provide some additional rationale for why we believe that the mixed (or base case) population is appropriate for decision making. **Standard of care as a comparator** We agree with the committee that standard of care (SoC) is not the only comparator in the base case population, as evidenced by our providing comparisons to mepolizumab and reslisumab in their respective NICE recommended populations, where each is a subset of the base case population; however, we maintain that SoC is still a relevant comparator in the whole of the base case population	Thank you for your comments. The committee discussed the appropriateness of the mixed population to decision making and considered the comparison with standard in this mixed population. They did not consider the comparison of the mixed population with standard care suitable for decision making and more appropriate to consider the clinical and cost effectiveness of benralizumab in relation to eligibility of patients for other treatments available in the NHS based on the severity of disease defined by oral corticosteroid use, eosinophil count and the number of exacerbations, rather than considering standard care alone an appropriate comparator for all patients. The committee's considerations are outlined in sections 3.5-3.9 and 3.13 of the FAD.

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			and not solely in the non-biologic eligible population. As demonstrated in our previous ACD response, standard of care is still used in the majority of patients who meet the eligibility criteria for the mepolizumab NICE recommended patient population (at least 84.5% - with IMS data showing that 1,677* patients at end of March 2018 were receiving mepolizumab out of 10,798** eligible patients according to NICE criteria) and in those patients who meet the eligibility criteria for the reslizumab NICE recommended patient population (only 39* patients were receiving reslizumab in the UK at end of March 2018 out of 25,606*** patients eligible for reslizumab according to NICE criteria) while acknowledging that there is some overlap between these two populations. 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 the above, and the fact that the ACD clearly states that within both the mepolizumab and reslizumab NICE recommended populations “some (people) may choose standard of care” we believe that standard of care should be considered as a relevant comparator within the entirety of the base case population. Therefore, cost effectiveness results in this population for the comparison vs. standard of care should be the basis for decision making. * 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. ** Mepolizumab company submission, page 264, table 157. Scaled to account for change in EOS cut	

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*** Reslizumab company submission page 247, table 150

Generalisability to the NHS in England

The ACD states that “the company’s estimate on the proportion of people with exactly 3 exacerbations in response to the ACD was based on observational data, and was higher than the proportion in the trials that was used in the economic model”, and that “this cast further doubt on the generalisability of the proposed population”.

It should be noted that the percentage of patients with exactly 3 exacerbations (and not on mOCS) according to RWE presented by the company (31.2%) is given as a percentage of the entire base case population where a recommendation is sought i.e. those patients with 300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS.

The percentages of patients presented by the ERG (19.9% for both arms in SIROCCO and 24.7% and 22.6% for Q8W and placebo arms in CALIMA) are taken from the SIROCCO and CALIMA trial CSRs and are therefore given as a percentage of the entire trial primary end point populations (i.e. those patients with 300+ EOS; AND 2+ exacerbations in prior year) and not as a percentage of the base case population. Clearly these patient populations are not equivalent, and percentages which use different denominators should not be compared.

A like-for-like comparison is given in Table 1 below presenting a percentage of the base case population where a NICE recommendation is sought using either RWE (31.2%) or trial data (24.6%).

Note, the population with exactly 3 exacerbations (and not on mOCS) includes, but is not exclusive to, the non-biologic eligible population; and it should be noted that the non-biologic eligible population represents only 11.1% of the base-case population in the real-world, and 7.3% of the base-case population in the trial (see table below).

Table 1: Comparison of patient cohort size, RWE-based vs. trial based
<table>
<tr><td></td><td>Observational UK RWE</td><td></td></tr>
<tr><td></td><td>As % of base case population*</td><td>As po</td></tr>
<tr><td>People with 3 exacerbations, not taking oral corticosteroids with an eosinophil count of 300 or more</td><td>31.2%</td><td></td></tr>
<tr><td>People with 3 exacerbations, not taking oral corticosteroids with an eosinophil count of 300-399 (non-biologic eligible population)</td><td>11.1%</td><td></td></tr>
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*note this assumes that 54.1% of patients are receiving mOCS
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			We expect this difference (31.2% vs. 24.6%) to have minimal impact on the cost-effectiveness of benralizumab in the real-world. **Precedent in previous appraisals** In the previous NICE appraisals of mepolizumab and reslizumab, it was accepted by the committee that mixed populations would be appropriate for decision making, despite different severities of disease within these populations having an impact on the cost effectiveness of these treatments. Firstly, during the mepolizumab appraisal an ICER of £78,716 (ID798: Response to ERG questions – mepolizumab for severe refractory eosinophilic asthma page 52) for the subgroup population of patients with ≥150 EOS AND <4 exacerbations AND being on mOCS was reported (the ICER in the full mixed population at this stage being £19,526). While it must be acknowledged that this ICER was reported prior to the PAS for mepolizumab being finalised, it does demonstrate that mepolizumab would be less cost effective within this population than in the full mixed population and as mepolizumab was recommended in this mixed population with a final ICER of £29,163 it is unlikely that mepolizumab would have been cost effective within the subgroup. Secondly, during the reslizumab appraisal, scenario analyses were presented which demonstrated that reslizumab was more cost effective within a population of patients with 400+ eosinophils, AND 4+ exacerbations in prior year, than in the full mixed population of patients with 400+ eosinophils, AND 3+ exacerbations in prior year (TA479 - appraisal consultation 2, committee papers, p30 Table 8). Again, given that reslizumab was approved in a population of patients with 400+ eosinophils, AND 3+ exacerbations in prior year with an ICER of £29,870, and is more cost effective in patients with 4+ exacerbations it is therefore unlikely that reslizumab would have been cost effective in a population of patients with exactly 3 exacerbations. Given that NICE has on both of these occasions accepted a mixed population to be appropriate for decision making, we request that a similar approach is taken for this appraisal. For the reasons given above, therefore, 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). As requested by NICE, we have calculated the cost-effectiveness for benralizumab vs. SoC in patients with 300-399 EOS, (exactly) 3 exacerbations in the prior year, who are not taking oral corticosteroids, a population eluded to in the ACD and the only population for which SOC is the only comparator as these patients do not meet the NICE criteria for mepolizumab or reslizumab.	Comment noted. In the mepolizumab and reslizumab appraisals optimised recommendations were made in a population who were more severe (defined by blood eosinophil levels and the exacerbation rate) where it was more clinically and cost effective.
12			**Model Inputs**	Thank you for your comments. This new evidence was

No.	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	Company	AstraZeneca	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]). The majority of inputs, including mortality inputs are now aligned with those of the ERG base case. There are only two inputs for which we have included different inputs to the ERG. These are described below with the rationale given. Percentage of patients on mOCS at baseline The ACD states that there is considerable uncertainty about the proportion of people taking maintenance oral corticosteroids at baseline. The ERG base case again includes a figure of 41.7% of patients being on mOCS at baseline, for both populations (base case population with a comparator of SOC; and mepolizumab-eligible population with a comparator of mepolizumab), which is sourced from Heaney et al. However, as raised by the clinical expert at the second committee meeting 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 therefore 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). We further believe that there has been some misunderstanding on the source of this figure as the ERG member raised that they could not verify this figure from the reported source. To clarify, this figure was obtained from a sub analysis of a UK AstraZeneca sponsored study and therefore is not available in the public domain. In order to clear up any confusion surrounding this figure, we provide the raw data upon which it is calculated in Table 2 below. **Table 2: Numbers of patients by EOS count, OCS status and exacerbation history from Kerkhoff et al (note sample data, unprojected)**	considered by the committee and its considerations are outlined in sections 3.10- 3.11 of the FAD.

No.	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row						NICE Response Please respond to each comment
			Number of exacerbations in prior year	Number of OCS prescriptions	≥200 EOS	≥300 EOS	≥400 EOS	≥500 EOS	
			0	<6	[redacted]	[redacted]	[redacted]	[redacted]	
				≥6	[redacted]	[redacted]	[redacted]	[redacted]	
			1	<6	[redacted]	[redacted]	[redacted]	[redacted]	
				≥6	[redacted]	[redacted]	[redacted]	[redacted]	
			≥1	<6	[redacted]	[redacted]	[redacted]	[redacted]	
				≥6	[redacted]	[redacted]	[redacted]	[redacted]	
			<2	<6	[redacted]	[redacted]	[redacted]	[redacted]	
				≥6	[redacted]	[redacted]	[redacted]	[redacted]	
			≥2	<6	[redacted]	[redacted]	[redacted]	[redacted]	
				≥6	[redacted]	[redacted]	[redacted]	[redacted]	
			≥3	<6	[redacted]	[redacted]	[redacted]	[redacted]	
				≥6	[redacted]	[redacted]	[redacted]	[redacted]	
			≥4	<6	[redacted]	[redacted]	[redacted]	[redacted]	

No.	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

	≥6	[redacted]	[redacted]	[redacted]		[redacted]
≥5	<6	[redacted]	[redacted]	[redacted]		[redacted]
	≥6	[redacted]	[redacted]	[redacted]		[redacted]

The table shows the number of patients within the study who are adults, on a high dose ICS/LABA and are then subdivided by their EOS count, OCS status (being on mOCS being defined as a minimum of 6 months continuous use of OCS) and number of exacerbations at baseline.

As shown in the table the base case population is made up of those patients with an EOS count of ≥300 and an exacerbation history of ≥3 and <6 mOCS prescriptions (the orange box) plus those patients with an EOS count of ≥300 and an exacerbation history of <2 or ≥2 and ≥6 mOCS prescriptions (the green boxes).

The total analysis population therefore who would meet the criteria for the base case population would be 5,247, of which 2,838 would be receiving mOCS, (unprojected sample data) yielding a percentage of 54.1% of patients receiving mOCS at baseline.

Further, in the mepolizumab NICE reimbursed population this total population would be reduced to 3,612 (the red box plus the green boxes) of which 2,838 would be receiving mOCS, yielding a percentage of 78.6% of patients receiving mOCS at baseline.

As specified below, we have used a lower percentage of 60% in the mepolizumab NICE reimbursed population, which we consider to be conservative.

We believe our figures to be further validated as the clinical experts at the meeting suggested that a figure of between 66% to80% 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 66% 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, for this reason we feel the use of 54.1% is appropriate.

<u>Administration time</u>

<table>
<tr><th>No.</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>During the discussion at the first 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, one of 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 3: 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>% patients on mOCS</td><td>54.1% in the base case population

60% in the mepolizumab NICE recommended population</td><td>As per UK RWE

As per base case at A</td></tr>
<tr><td>Administration time</td><td>5 minutes for benralizumab

20 minutes for mepolizumab</td><td>As per first committee clinical expert opinion</td></tr>
<tr><td colspan="3">All other model inputs remain as in manufacturer base case from ACD1 (i.e. other inputs are aligned w case)</td></tr>
</table></td><td></td></tr>
<tr><td>13</td><td>Company</td><td>AstraZeneca</td><td>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 £25,192, as shown in Table 4 below.

Table 4: 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 QA</th></tr>
</table></td><td>Thanks you for your comments. The committee's considerations about the company's cost-effectiveness results incorporating the revised patient access scheme are detailed in the FAD. (see section 3.14-3.16 of the FAD).</td></tr>
</table>

No.	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Base Case	**Benralizumab**	[redacted]	[redacted]	[redacted]	[redacted]		**£25,192**
	SoC	[redacted]		[redacted]			

Table 5 below shows the revised cost effectiveness analysis vs. mepolizumab (using mepolizumab list price) in the mepolizumab NICE recommended population (300+ EOS; AND either 4+ exacerbations in prior year OR receiving maintenance OCS).

Table 5: Cost effectiveness results vs. mepolizumab in mepolizumab NICE reccommended population*

Scenario		Total cost	Δ cost	Total QALYs	Δ QA
Base Case	**Benralizumab**	[redacted]	[redacted]	[redacted]	
	Mepolizumab	[redacted]		[redacted]	

*Benralizumab net price vs. mepolizumab list price

Table 6 below shows the revised cost effectiveness analysis vs. reslizumab (using reslizumab list price) in the reslizumab NICE recommended population (400+ EOS; AND 3+ exacerbations in prior year).

Table 6: Cost effectiveness results vs. reslizumab in reslizumab NICE recommended population*

Scenario		Total cost	Δ cost	Total QALYs	Δ QA
Base Case	**Benralizumab**	[redacted]	[redacted]	[redacted]	
	Reslizumab	[redacted]		[redacted]	

*Benralizumab net price vs reslizumab list price

Table 7 below shows the revised cost effectiveness analysis vs. SoC in the non-biologic eligible population (300-399 EOS; AND 3 exacerbations in prior year). See appendix 1 for further detail on clinical and utility inputs. We reiterate our above-stated belief that it is not appropriate to segment the base case population in this way and that the basis for decision-making should be comparison to SOC in the entire base case population, as was the case in the appraisals of mepolizumab and reslizumab.

Table 7: Cost effectiveness results vs. SoC in the non-biologic eligible population

No.	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Scenario		Total cost	Δ cost	Total QALYs	Δ QALYs	ICER
Base Case	Benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£38,304
	SoC	[redacted]		[redacted]		

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 Monday 6th August 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:	[redacted]

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, and kindly asks the committee to consider the following key points:

1. AstraZeneca has **revised the Patient Access Scheme (PAS)** to reduce the price of benralizumab to £[redacted] per vial (previously £[redacted]) with the objective of being cost effective vs mepolizumab confidential net price.

2. AstraZeneca is seeking a recommendation for a sub-group of the licensed patient population who will benefit the most from benralizumab, as per trial results. This requested population is the **same population as initially submitted** and is defined as follows: 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. For clarity, we will refer to this population in this document as the "base case population".

   Data from the registrational studies shows increased benefit for the base-case population vs the ITT population: exacerbation reductions of 53% 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.

3. With the revised PAS, the cost-effectiveness results are as follows:
   - **The ICER vs SOC in the base-case population where a recommendation is sought is £25,192. We consider the ICER in this population vs SOC to be the basis for decision making,** because SOC is a relevant comparator for the entire "base case population", and therefore it is not appropriate to divide this population into sub-groups for the comparison vs SOC (see detailed rationale in the technical response later in this document).
   - In the mepolizumab NICE recommended population, benralizumab is dominant versus mepolizumab (benralizumab net price vs mepolizumab **list** price)
   - In the reslizumab NICE recommended population, benralizumab is dominant versus reslizumab (benralizumab net price vs reslizumab **list** price)
   - As requested by NICE, we have calculated the ICER vs SOC in the current "non-biologic eligible" segment of the base-case population (300-399 EOS; AND exactly 3 exacerbations in prior year), which is £38,304. As described in the technical response, we believe that the primary ICER for decision making should be the ICER for the entire mixed, base-case population because:
     a) SOC is a comparator for the entire base-case population,
     b) The cost-effectiveness results are generalisable to real-world clinical practice in the NHS in England; and
     c) There is past precedent for using a mixed-population approach for decision making in the mepolizumab and reslizumab appraisals.

4. **There is strong clinical support for final NICE guidance to be issued for benralizumab in a broader population than the current ACD proposal,** and clinical opinion that prescribing of mepolizumab and benralizumab (in suitable patients according to NICE guidance criteria) should be open to prescriber choice. Of 20 clinical experts who shared their views on the ACD with AstraZeneca on these specific topics and gave consent to be included in this response[1], 20

stated the need for benralizumab NICE guidance in a broader population than that proposed by the ACD, and 20 stated that prescribing of mepolizumab and benralizumab (according to NICE guidance criteria) should be open to prescriber choice (i.e. No pre-defined sequencing).

5. Benralizumab provides **significant benefits** to patients and their families/carers compared with mepolizumab and reslizumab:

- 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 requires **less frequent dosing**, which could have a significant impact on patients' adherence to treatment, their quality of life, and on their families/carers. Benralizumab is administered every 8 weeks (after the first 3 doses which are administered every 4 weeks), compared with mepolizumab and reslizumab, which are administered every 4 weeks. Clinicians at the first appraisal committee meeting mentioned that benralizumab therefore meets a specific unmet need in the patient population who prefer to receive biologic treatment less frequently.
- [redacted]

6. Benralizumab will provide **productivity benefits** compared with mepolizumab and reslizumab, for patients receiving their biologic in the clinic.
Productivity benefits have not been included in the cost effectiveness analysis, and are provided here as additional information, which the committee may wish to consider.
Patients may require time off work to travel to and from the severe asthma clinic to receive a biologic. If we assume that on average a patient would require a half day (4 hours) off work to travel to and from the clinic, a patient on mepolizumab would require 52 hours (4*13 doses) off work each year compared with 26 hours off work (4*6.5 doses) each year for a patient on benralizumab (from year 2 onwards). Using the average earnings in the UK and having accounted for discontinuation and discounting, this means that for a working patient on benralizumab there is a productivity benefit of £1,684 on average over the lifetime compared with a working patient on mepolizumab (using a retirement age of 66). If we assume 50% of severe, eosinophilic asthma patients are working, this equates to a productivity benefit per benralizumab patient of £842 over the lifetime compared with a patient receiving mepolizumab.

[redacted]

Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

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[redacted]

Based on the above points and the technical information below, we ask the committee to grant a recommendation for benralizumab in the base case 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 all of these patients have access to the specific benefits of benralizumab.

Your sincerely,

[redacted]
AstraZeneca UK Country President

1 AstraZeneca approached 54 severe asthma specialists in the UK to ask for their views on the ACD. 26 of these did not share their views with AstraZeneca (13 did not respond to the initial email or were not available to speak to AstraZeneca, 1 was off sick, 1 was on holiday, 1 did not have enough time, 3 had not yet seen the consultation so did not feel able to comment, 6 did not want their views included within this response as they were responding directly to NICE, 1 wanted to wait for the SMC decision before commenting). Of the 28 who shared their views, 8 did not give consent for AstraZeneca to include their anonymised views within this response.

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Benralizumab for treating severe eosinophilic asthma [ID1129]

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A. Appropriateness of the mixed population to decision making

The ACD for benralizumab for the treatment of severe asthma states that "The mixed population compared with standard care is not appropriate for the purposes of decision making" for the following reasons:

1. Standard of care is not the only comparator in this population
2. There is major doubt about the generalisability to the NHS in England

Below we seek to address these points as well as provide some additional rationale for why we believe that the mixed (or base case) population is appropriate for decision making.

Standard of care as a comparator

We agree with the committee that standard of care (SoC) is not the only comparator in the base case population, as evidenced by our providing comparisons to mepolizumab and reslisumab in their respective NICE recommended populations, where each is a subset of the base case population; however, we maintain that SoC is still a relevant comparator in the whole of the base case population and not solely in the non-biologic eligible population.

As demonstrated in our previous ACD response, standard of care is still used in the majority of patients who meet the eligibility criteria for the mepolizumab NICE recommended patient population (at least 84.5% - with IMS data showing that 1,677* patients at end of March 2018 were receiving mepolizumab out of 10,798** eligible patients according to NICE criteria) and in those patients who meet the eligibility criteria for the reslizumab NICE recommended patient population (only 39* patients were receiving reslizumab in the UK at end of March 2018 out of 25,606*** patients eligible for reslizumab according to NICE criteria) while acknowledging that there is some overlap between these two populations.

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 the above, and the fact that the ACD clearly states that within both the mepolizumab and reslizumab NICE recommended populations "some (people) may choose standard of care" we believe

that standard of care should be considered as a relevant comparator within the entirety of the base case population. Therefore, cost effectiveness results in this population for the comparison vs. standard of care should be the basis for decision making.

* 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.

** Mepolizumab company submission, page 264, table 157. Scaled to account for change in EOS cut off

*** Reslizumab company submission page 247, table 150

Generalisability to the NHS in England

The ACD states that "the company's estimate on the proportion of people with exactly 3 exacerbations in response to the ACD was based on observational data, and was higher than the proportion in the trials that was used in the economic model", and that "this cast further doubt on the generalisability of the proposed population".

It should be noted that the percentage of patients with exactly 3 exacerbations (and not on mOCS) according to RWE presented by the company (31.2%) is given as a percentage of the entire base case population where a recommendation is sought i.e. those patients with 300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS.

The percentages of patients presented by the ERG (19.9% for both arms in SIROCCO and 24.7% and 22.6% for Q8W and placebo arms in CALIMA) are taken from the SIROCCO and CALIMA trial CSRs and are therefore given as a percentage of the entire trial primary end point populations (i.e. those patients with 300+ EOS; AND 2+ exacerbations in prior year) and not as a percentage of the base case population. Clearly these patient populations are not equivalent, and percentages which use different denominators should not be compared.

A like-for-like comparison is given in Table 1 below presenting a percentage of the base case population where a NICE recommendation is sought using either RWE (31.2%) or trial data (24.6%).

Note, the population with exactly 3 exacerbations (and not on mOCS) includes, but is not exclusive to, the non-biologic eligible population; and it should be noted that the non-biologic eligible population represents only 11.1% of the base-case population in the real-world, and 7.3% of the base-case population in the trial (see table below).

Table 1: Comparison of patient cohort size, RWE-based vs. trial based

	Observational UK RWE	SIROCCO/CALIMA
	As % of base case population*	As % of base case population*
People with 3 exacerbations, not taking oral corticosteroids with an eosinophil count of 300 or more	31.2%	24.6%
People with 3 exacerbations, not taking oral corticosteroids with an eosinophil count of 300-399 (non-biologic eligible population)	11.1%	7.3%

*note this assumes that 54.1% of patients are receiving mOCS

We expect this difference (31.2% vs. 24.6%) to have minimal impact on the cost-effectiveness of benralizumab in the real-world.

Precedent in previous appraisals

In the previous NICE appraisals of mepolizumab and reslizumab, it was accepted by the committee that mixed populations would be appropriate for decision making, despite different severities of disease within these populations having an impact on the cost effectiveness of these treatments.

Firstly, during the mepolizumab appraisal an ICER of £78,716 (ID798: Response to ERG questions – mepolizumab for severe refractory eosinophilic asthma page 52) for the subgroup population of patients with ≥150 EOS AND <4 exacerbations AND being on mOCS was reported (the ICER in the full mixed population at this stage being £19,526). While it must be acknowledged that this ICER was reported prior to the PAS for mepolizumab being finalised, it does demonstrate that mepolizumab would be less cost effective within this population than in the full mixed population and as mepolizumab was recommended in this mixed population with a final ICER of £29,163 it is unlikely that mepolizumab would have been cost effective within the subgroup.

Secondly, during the reslizumab appraisal, scenario analyses were presented which demonstrated that reslizumab was more cost effective within a population of patients with 400+ eosinophils, AND 4+ exacerbations in prior year, than in the full mixed population of patients with 400+ eosinophils, AND 3+ exacerbations in prior year (TA479 - appraisal consultation 2, committee papers, p30 Table 8). Again, given that reslizumab was approved in a population of patients with 400+ eosinophils, AND 3+ exacerbations in prior year with an ICER of £29,870, and is more cost effective in patients with 4+ exacerbations it is therefore unlikely that reslizumab would have been cost effective in a population of patients with exactly 3 exacerbations.

Given that NICE has on both of these occasions accepted a mixed population to be appropriate for decision making, we request that a similar approach is taken for this appraisal.

For the reasons given above, therefore, 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). As requested by NICE, we have calculated the cost-effectiveness for benralizumab vs. SoC in patients with 300-399 EOS, (exactly) 3 exacerbations in the prior year, who are not taking oral corticosteroids, a population eluded to in the ACD and the only population for which SOC is the only comparator as these patients do not meet the NICE criteria for mepolizumab or reslizumab.

B. 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]).

Benralizumab for treating severe eosinophilic asthma [ID1129]

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The majority of inputs, including mortality inputs are now aligned with those of the ERG base case. There are only two inputs for which we have included different inputs to the ERG. These are described below with the rationale given.

Percentage of patients on mOCS at baseline

The ACD states that there is considerable uncertainty about the proportion of people taking maintenance oral corticosteroids at baseline.

The ERG base case again includes a figure of 41.7% of patients being on mOCS at baseline, for both populations (base case population with a comparator of SOC; and mepolizumab-eligible population with a comparator of mepolizumab), which is sourced from Heaney et al. However, as raised by the clinical expert at the second committee meeting 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 therefore 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).

We further believe that there has been some misunderstanding on the source of this figure as the ERG member raised that they could not verify this figure from the reported source. To clarify, this figure was obtained from a sub analysis of a UK AstraZeneca sponsored study and therefore is not available in the public domain. In order to clear up any confusion surrounding this figure, we provide the raw data upon which it is calculated in Table 2 below.

Benralizumab for treating severe eosinophilic asthma [ID1129]

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Table 2: Numbers of patients by EOS count, OCS status and exacerbation history from Kerkhoff et al (note sample data, unprojected)

Number of exacerbations in prior year	Number of OCS prescriptions	≥200 EOS	≥300 EOS	≥400 EOS	≥500 EOS
0	<6	[redacted]	[redacted]	[redacted]	[redacted]
	≥6	[redacted]	[redacted]	[redacted]	[redacted]
1	<6	[redacted]	[redacted]	[redacted]	[redacted]
	≥6	[redacted]	[redacted]	[redacted]	[redacted]
≥1	<6	[redacted]	[redacted]	[redacted]	[redacted]
	≥6	[redacted]	[redacted]	[redacted]	[redacted]
<2	<6	[redacted]	[redacted]	[redacted]	[redacted]
	≥6	[redacted]	[redacted]	[redacted]	[redacted]
≥2	<6	[redacted]	[redacted]	[redacted]	[redacted]
	≥6	[redacted]	[redacted]	[redacted]	[redacted]
≥3	<6	[redacted]	[redacted]	[redacted]	[redacted]
	≥6	[redacted]	[redacted]	[redacted]	[redacted]
≥4	<6	[redacted]	[redacted]	[redacted]	[redacted]
	≥6	[redacted]	[redacted]	[redacted]	[redacted]
≥5	<6	[redacted]	[redacted]	[redacted]	[redacted]
	≥6	[redacted]	[redacted]	[redacted]	[redacted]

The table shows the number of patients within the study who are adults, on a high dose ICS/LABA and are then subdivided by their EOS count, OCS status (being on mOCS being defined as a minimum of 6 months continuous use of OCS) and number of exacerbations at baseline.

As shown in the table the base case population is made up of those patients with an EOS count of ≥300 and an exacerbation history of ≥3 and <6 mOCS prescriptions (the orange box) plus those patients with an EOS count of ≥300 and an exacerbation history of <2 or ≥2 and ≥6 mOCS prescriptions (the green boxes).

The total analysis population therefore who would meet the criteria for the base case population would be 5,247, of which 2,838 would be receiving mOCS, (unprojected sample data) yielding a percentage of 54.1% of patients receiving mOCS at baseline.

Further, in the mepolizumab NICE reimbursed population this total population would be reduced to 3,612 (the red box plus the green boxes) of which 2,838 would be receiving mOCS, yielding a percentage of 78.6% of patients receiving mOCS at baseline.

As specified below, we have used a lower percentage of 60% in the mepolizumab NICE reimbursed population, which we consider to be conservative.

We believe our figures to be further validated as the clinical experts at the meeting suggested that a figure of between 66% to 80% 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 66% 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, for this reason we feel the use of 54.1% is appropriate.

Administration time

During the discussion at the first 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, one of 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 3: Summary of economic model inputs

Input	Value	Justification
Price of benralizumab	£[redacted] per vial	Revised PAS
% patients on mOCS	54.1% in the base case population 60% in the mepolizumab NICE recommended	As per UK RWE

	population	As per base case at ACD1.
Administration time	5 minutes for benralizumab 20 minutes for mepolizumab	As per first committee meeting clinical expert opinion
All other model inputs remain as in manufacturer base case from ACD1 (i.e. other inputs are aligned with ERG's base case)		

C. 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 £25,192, as shown in Table 4 below.

Table 4: 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]	£25,192
	SoC	[redacted]		[redacted]		

Table 5 below shows the revised cost effectiveness analysis vs. mepolizumab (using mepolizumab list price) in the mepolizumab NICE recommended population (300+ EOS; AND either 4+ exacerbations in prior year OR receiving maintenance OCS).

Table 5: 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

Table 6 below shows the revised cost effectiveness analysis vs. reslizumab (using reslizumab list price) in the reslizumab NICE recommended population (400+ EOS; AND 3+ exacerbations in prior year).

Table 6: Cost effectiveness results vs. reslizumab in reslizumab NICE recommended population*

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

	Reslizumab	[redacted]		[redacted]		

*Benralizumab net price vs reslizumab list price

Table 7 below shows the revised cost effectiveness analysis vs. SoC in the non-biologic eligible population (300-399 EOS; AND 3 exacerbations in prior year). See appendix 1 for further detail on clinical and utility inputs. We reiterate our above-stated belief that it is not appropriate to segment the base case population in this way and that the basis for decision-making should be comparison to SOC in the entire base case population, as was the case in the appraisals of mepolizumab and reslizumab.

Table 7: Cost effectiveness results vs. SoC in the non-biologic eligible population

Scenario		Total cost	Δ cost	Total QALYs	Δ QALYs	ICER
Base Case	**Benralizumab**	[redacted]	[redacted]	[redacted]	[redacted]	**£38,304**
	SoC	[redacted]		[redacted]		

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Appendix 1 – Clinical and utility inputs for the non-biologic eligible population

Table 8: Efficacy in the pooled SIROCCO and CALIMA subgroup analysis

Estimate, 95% CI	Benralizumab 30mg Q8W (N=16)	Placebo (N=14)
Marginal annual exacerbation rate	0.51 (0.15,1.46)	1.26 (0.54,2.74)
Rate ratio	0.39 (0.10,1.54)	
P value	0.178	

Table 9: Transition probabilities – benralizumab, non-biologic eligible Population, 0-52 weeks

		Visit i+1			
		Controlled	**Uncontrolled**	**Exacerbation (Controlled)**	**Exacerbation (Uncontrolled)**
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 10: Transition probabilities – benralizumab, non-biologic eligible Population, >52 weeks

		Visit i+1			
		Controlled	**Uncontrolled**	**Exacerbation (Controlled)**	**Exacerbation (Uncontrolled)**
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

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Table 11: Transition probabilities – SoC, non-biologic eligible Population, all weeks

		Visit i+1			
		Controlled	**Uncontrolled**	**Exacerbation (Controlled)**	**Exacerbation (Uncontrolled)**
Visit i	Controlled	[redacted]	[redacted]	[redacted]	[redacted]
	Uncontrolled	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
	Exacerbation (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Exacerbation (Controlled) refers to an exacerbation from the previous state of Controlled, Exacerbation (Uncontrolled) refers to an exacerbation from the previous state of Uncontrolled.

Table 12: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	Derivation
Controlled, non mOCS, benralizumab	0.8868 (0.05176)	Mapped EQ-5D-3L values from directly observed EQ-5D-5L values in pooled SIROCCO/CALIMA trials
Controlled, non mOCS, SoC	0.8901 (0.04734)	
Uncontrolled, non mOCS, benralizumab	0.7699 (0.05574)	Mapped EQ-5D-3L values from directly observed EQ-5D-5L values in pooled SIROCCO/CALIMA trials
Uncontrolled, non mOCS, SoC	0.7618 (0.04250)	
Exacerbation, OCS (burst) prior HS Controlled, non mOCS	0.7913 (0.03732)	Mapped EQ-5D-3L values from directly observed EQ-5D-5L values in pooled SIROCCO/CALIMA trials
Exacerbation, A+E, prior HS Controlled, non mOCS	0.7913 (0.03732)	
Exacerbation, Hospitalised prior HS Controlled, non mOCS	0.6413 (0.05285)	Mapped EQ-5D-3L values from directly observed EQ-5D-5L values in pooled SIROCCO/CALIMA trials, base case population values used due to low numbers in subgroup
Exacerbation OCS (burst), prior HS Uncontrolled, non mOCS	0.8612 (0.02678)	Mapped EQ-5D-3L values from directly observed EQ-5D-5L values in pooled SIROCCO/CALIMA trials
Exacerbation, A+E, prior HS Uncontrolled, non mOCS	0.8612 (0.02678)	
Exacerbation, Hospitalised prior HS Uncontrolled, non mOCS	0.6413 (0.05285)	Mapped EQ-5D-3L values from directly observed EQ-5D-5L values in pooled SIROCCO/CALIMA trials, base case population values used due to low numbers in subgroup

References

IQVIA , BPI/HPA Combined data set, March 2018.

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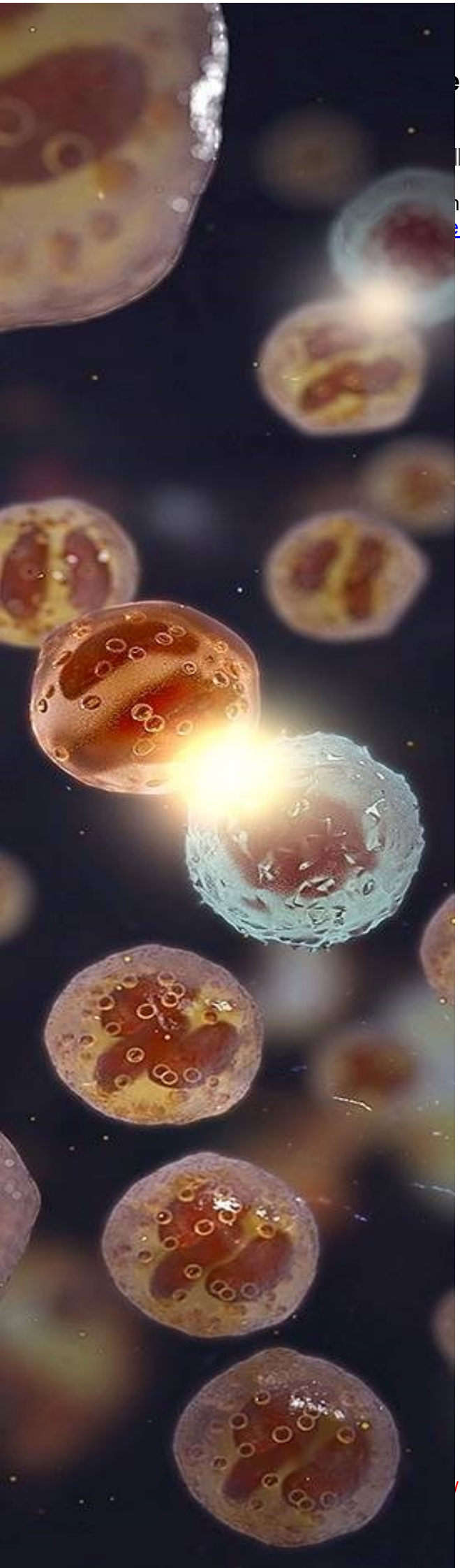

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we 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.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Association of Respiratory Nurse Specialists**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Nothing to disclose**]
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Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that the evidence that is available on benralizumab has not been applied within this guidance.
2	The two studies on benralizumab (SIROCCO and CALIMA) used an eosinophil count of 300 for study entry not 400 as NICE are recommending
3	The analysis from these studies demonstrated that patients with an eosinophil count of 300 or higher along with 3 exacerbations in the previous 12 months had a positive response.
4	We feel the criteria should include patients who have had 3 or more exacerbations within the previous 12 months OR those also on continuous oral steroids.
5	The eosinophil count for mepolizumab treatment is 300 and you suggest that people for benralizumab is 400. If someone is on mepolizumab it will invariably lower their eosinophil count. How can you then switch to benralizumab, does the patient have to have a break from treatment altogether and wait for their eosinophil count to rise to 400 before being allowed to have benralizumab? This surely would not be ethically or morally correct.
6	We would ask that NICE reconsider these guidelines based on the evidence currently available.

Insert extra rows as needed

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- 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.
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Example 1	We are concerned that this recommendation may imply that the drug would only be considered second line to Mepolizumab, even if the drugs were equally cost effective, in the final approval. As Benralizumab appears to have greater efficacy, with trial evidence of impact on lung function and quality of life, over and above the reductions seen in exacerbations, then this would be a disadvantageous position. The practical advantage of eight weekly injections, will also have cost to the nation savings, even though this is not calculated completely in NICE assessment.
1	***Has all of the relevant evidence been taken into account?*** We are uncertain if the work by FitzGerald et al. Lancet Respir Med. 2018 Jan;6(1):51-64, has been considered – this specifically looks at predictors of enhanced response with benralizumab.
2	***Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?*** Despite ZONDA, SIROCCO and CALIMA being accounted for, it still not clear why an eosinophil cut off of 400 cells/uL is chosen based on clinical evidence. Cost appears to be the only reason for this arbitrary number essentially displacing reslizumab therapy. This drug will already be poised as second line to mepolizumab based on the NICE recommendations. The 400cell/uL would discriminate against patients who reflect the trial populations may potentially lose out. We are also concerned about the timescale placed on eosinophil counts – from this draft guidance: - the blood eosinophil count has been recorded as 400 cells per microlitre or more in the past 12 months Many of the most patients who stand to benefit most from these treatments have eosinophil counts suppressed by oral steroids. Additional disadvantage will be set for patients who have originally been trialled on Mepolizumab, where there is clear evidence of the ability to suppress eosinophils but with some patients not gaining clinical benefit. We strongly believe the phrase should be at worst….eosinophilic in the last 12 months, or in the case of patients who have already received an unsuccessful trial of Mepolizumab…then were demonstrated to have eosinophils above 300 cell per microliter in the 12 months prior to their initial trial of Mepolizumab.
3	***Are the recommendations sound and a suitable basis for guidance to the NHS?*** No. We strongly disagree with the draft recommendation that benralizumab is recommended for a narrow population of people with blood eosinophils of 400 or

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	more with at least 3 exacerbations in the last 12 months in whom mepolizumab is not an option. The summaries of clinical effectiveness used to generate this patient group suggested in the ACD are not reasonable interpretations of the evidence. We feel that the current provisional recommendations are not sound and are not a suitable basis for guidance to the NHS.
4	***Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity.*** Unknown.

Insert extra rows as needed

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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.	None
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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 5pm on 06/08/2018 **please return via** NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We believe the proposed population on which a draft positive recommendation has been issued for benralizumab represents a balanced reflection of the evidence presented throughout the appraisal process to date. The proposed population seeks to reflect where benralizumab has demonstrated value to the NHS and severe asthma patients relative to current NICE guidance in place for reslizumab and mepolizumab. The following comments highlight our ongoing concerns regarding: • The specificity of the proposed NICE guidance wording and possible consequences of its future implementation in practice • The conclusions drawn on the application of the comparative effectiveness of benralizumab versus mepolizumab • Limited additive benefit offered by benralizumab over current NICE recommended anti-IL5's
2	**The description of the proposed NICE benralizumab guidance needs to be defined further to ensure its *appropriate* usage in clinical practice – 'where mepolizumab is not a treatment option'** The current draft guidance wording stipulates '*and mepolizumab is not a treatment option*'. We strongly request that this wording is re-considered by the Committee and altered to '*and where an individual is ineligible for mepolizumab based on clinical criteria or has previously not adequately responded to mepolizumab'*. As the Committee is aware, NHS England directly commissions the Specialised Respiratory Services for Severe Asthma (adults) including the delivery of biologic therapy. One of the key roles of the specialist centres is to improve outcomes for people with severe asthma and to act as clinical gatekeepers to ensure appropriate access to high cost technologies (including biological agents), to prevent inappropriate use, unnecessary risk to patients and cost-effective use of resources to the NHS. Currently, to access a NICE recommended biologic therapy, a form (via the Blueteq system) must be completed. This sets out the NICE guidance criteria and we understand this is a series of tick boxes. We believe the implementation of the draft guidance wording '*and mepolizumab is not a treatment option*' via the Blueteq system is ambiguous for implementation and may be open to interpretation by clinicians, beyond the clinical and cost-effectiveness evidence appraised by NICE. This may subsequently lead to an unanticipated larger population likely to receive benralizumab than that defined in the final NICE guidance, inclusive of patient subgroups not shown to be cost-effective. A further consequence of this, is an increase in the overall budget impact which the specialised service is set up to gate keep. We recognise the need expressed by patients and clinicians for further treatment options for severe eosinophilic asthma, however we are concerned that the current draft guidance wording could indicate acceptance for benralizumab to be prescribed earlier in the treatment pathway and ahead of mepolizumab unless the draft guidance wording clearly states '*and*

	where an individual is ineligible for mepolizumab based on clinical criteria or has previously not adequately responded to mepolizumab'. Throughout the appraisal process the Committee has been clear in their conclusions - benralizumab has not demonstrated a cost-effective proposition compared with mepolizumab. This is owed to highly uncertain comparative efficacy derived through a matching adjusted indirect comparison as well as greater overall cost savings offered by the mepolizumab patient access scheme. We want to ensure that any future guidance recommendations for benralizumab clearly reflects the appraisal of the evidence presented to support its later fair application within the NHS.
3	**The description of the proposed NICE benralizumab guidance needs to be defined further to ensure its *appropriate* usage in clinical practice - *'at least 3 exacerbations in the past 12 months'*** The current draft guidance recommendation for benralizumab states: *'The person ……has had at least 3 asthma exacerbations in the past 12 months'* We believe the Committee need to be aware of the possible implications in clinical practice if the current draft guidance wording remains in place. Based on the evidence appraised, we agree with the Committee's proposed population given the conclusions of the Committee in ACD2. We agree that in patients: • Blood eosinophil count ≥300 cells/μL, ≥3 exacerbations, not on maintenance oral corticosteroids – conclusion cannot be drawn as the ICER has not been presented • Blood eosinophil count ≥400 cells/μL, ≥3 exacerbations, not on maintenance oral corticosteroids – benralizumab is cost-effective compared with reslizumab and standard of care • Blood eosinophil count ≥300 cells/μL, ≥4 exacerbations, and / or on maintenance oral corticosteroids – benralizumab is not cost-effective compared with mepolizumab The future guidance recommendation will be used to develop the criteria captured via the Blueteq system for biologic access in tertiary care centres. Whilst we understand that NICE do not have a role in the development of future Blueteq criteria, further detail in the final guidance wording may help to address any ambiguity in clinical practice. Our suggested way to avoid the ambiguity is as follows: *'The person has agreed to and followed the optimised standard treatment plan, and **either:*** • *has had 3 asthma exacerbations needing systemic corticosteroids in the past 12 months or* • *at least 4 asthma exacerbations needing systemic corticosteroids and is ineligible for mepolizumab based on clinical criteria (or has previously not adequately responded to mepolizumab)'*
4	**The description of the proposed NICE benralizumab guidance needs to be defined further to ensure its *appropriate* usage in clinical practice – 'severe asthma exacerbations'** We seek clarification on the apparent change to the draft guidance wording stated in ACD2

	compared with that communicated to registered consultees and commentators on 26 June 2018 following the second Appraisal Committee Meeting. This is with respect to defining asthma exacerbations. The communication sent to registered consultees and commentators stated *'……the person has had 3 or more severe asthma exacerbations needing systemic corticosteroids in the past 12 months….*'. Whereas the draft guidance wording in ACD2 states '……*has had at least 3 asthma exacerbations in the past 12 months…*' The draft guidance wording could suggest that milder exacerbations (e.g. a worsening of symptoms without the need for treatment intervention) is credible criterium for consideration of benralizumab therapy. To align to the definition of an exacerbation in the benralizumab pivotal trials, CALIMA and SIROCCO, the assumptions the manufacturer has included within their cost-effectiveness modelling, and to ensure consistency of NICE guidance for all biologics in severe asthma, we believe this wording should be altered to: '….has had at least 3 severe asthma exacerbations *needing systemic corticosteroids in the past 12 months…'.* We believe the consistency is important for the local implementation of guidance for clinicians and patients.
5	**We agree with the Committee's conclusion that the method used to estimate the comparative effectiveness of benralizumab versus mepolizumab is not robust.** We agree with the Committee's conclusions with regards to the method of deriving and the presented results of the comparative effectiveness versus mepolizumab: • The rationale for the Matching Adjusted Indirect Comparison instead of a network meta-analysis of mepolizumab and reslizumab was not adequately justified • There remains uncertainty about the clinical effectiveness of benralizumab compared with mepolizumab (see comment 6). We shared our concerns in detail with respect to these points in addition to the overall conduct of the Matching Adjusted Indirect Comparison in the consultation to ACD1.
6	**We continue to strongly disagree that the relative efficacy between benralizumab and mepolizumab in the intention to treat populations can be applied to more severe sub-groups and believe this is supported by available published evidence for both mepolizumab and benralizumab.** The Committee stated that they heard from the manufacturer that the Matching Adjusted Indirect Comparison matched benralizumab patients to those in the mepolizumab trial and assumed that the relative difference in efficacy between the two treatments to be the same in the most severe subgroup as in the intention to treat population. As per our response to ACD1, we continue to strongly disagree that the relative efficacy between the two treatments in the intention to treat population can be applied to the most severe sub-populations and believe the published evidence for both treatments supports our disagreement. The published meta-analysis of MENSA and DREAM (Ortega et al., 2016) clearly shows

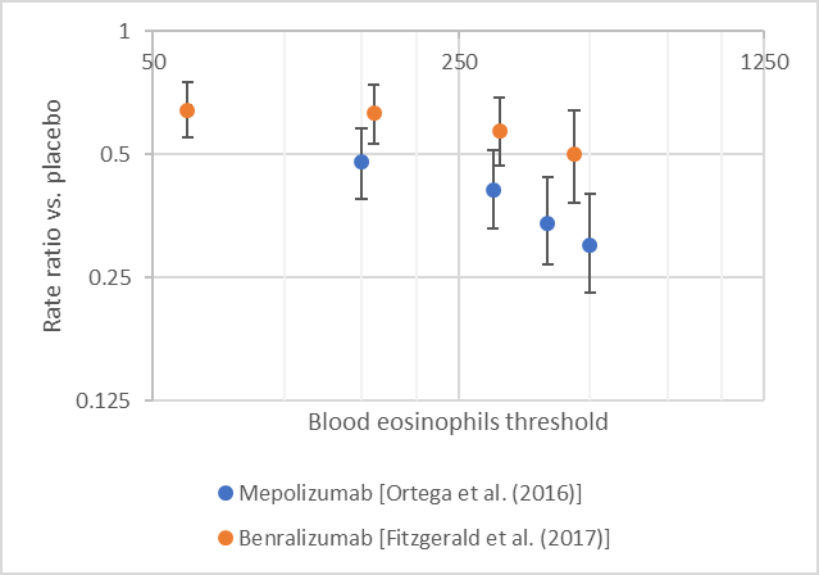
there is a dose response for add-on mepolizumab with increasing eosinophils at baseline. The reported rate ratio of mepolizumab vs. placebo for baseline eosinophils (EOS) is as follows:

- ≥ 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 effect estimates for mepolizumab (Ortega et al. 2016) and benralizumab (Fitzgerald et al., 2017) are presented below.



With increasing eosinophil 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.

Further, we refer the Committee to the EMA Preliminary Assessment Report for benralizumab, specifically to section 3.7.2 Balance of benefits and risks:

"Despite its dramatic effect on blood eosinophils benralizumab has demonstrated a modest effect on the frequency of exacerbations as reflected in relative terms by a ~40% reduction in the annual exacerbation rate and in absolute terms by a difference of about 0.5/year from 1.14 to 0.66/year. It is noteworthy that in similar patient populations, the two other anti-IL-5 agents (mepolizumab and reslizumab) achieved

	reductions in asthma exacerbations rates greater than 50% from a level of ~1.80/year." Source: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004433/WC500245333.pdf. Available online: [Accessed 24 July 2018]
7	**We agree with the NICE Committee, mepolizumab remains the relevant comparator for consideration in the mepolizumab NICE recommended population** We strongly agree with the Committee that mepolizumab and reslizumab are both the relevant comparators in this appraisal. However, we disagree that the uptake of mepolizumab should be considered low or lower than expected in the NICE mepolizumab population. The total population eligible for mepolizumab reflects *all* eligible patients irrespective of where they currently reside in the healthcare system; primary, secondary or tertiary care. The tertiary centres gatekeep access to mepolizumab and therefore the apparent uptake of mepolizumab may appear low as a percentage of all possible eligible patients. However, uptake of mepolizumab as a percentage of those patients eligible *and* referred to tertiary centres is higher. Further, as confirmed by the clinical expert on the committee, many severe asthma centres are still working through waiting lists of appropriate patients for mepolizumab. Therefore, we strongly agree with the Committee that in the NICE mepolizumab population, mepolizumab remains the key comparator for benralizumab.
8	**We believe the innovation offered by benralizumab will be of limited additive value for decision making purposes** *a) The benefit of dosing convenience offered by benralizumab is potentially short-lived* The Committee concluded that the dosing schedule for benralizumab would be beneficial for patients despite this not being captured within the cost-effectiveness analysis. GSK agrees with the Committee that reducing visits to hospital could be important for people with severe eosinophilic asthma. It is with the aim of reducing the burden of travel to hospitals for patients that **COMMERICAL IN CONFIDENCE INFORMATION REMOVED** *b) Long-term efficacy and safety of new therapies is of importance to patients choosing to commence biologic therapy – mepolizumab has substantial real-world evidence supporting its usage in practice.* As part of the treatment decision between a patient and their clinician there are many factors that need to be considered together and not in isolation. The Committee heard that some patients prefer not to receive biologic therapy because there is no long-term evidence on their use. We would like to remind the Committee that relative to reslizumab and benralizumab, the mepolizumab COSMOS and COLUMBA open-label extension studies have demonstrated that the safety and efficacy of mepolizumab was maintained for 1.5 years and 4.5 years respectively; with exacerbation reduction maintained and a safety profile reflective of earlier trials. This is in addition to the 15 months in which mepolizumab

	has been made available by the NHS. In this time patients have had the opportunity to take part in the REALITI-A registry study, which will generate real world evidence on mepolizumab outcomes and safety. Further the EMA's CHMP has recently recommended the use of mepolizumab in severe eosinophilic asthma paediatric and adolescent patients (≥ 6yrs - <18 years). *c) Dosing convenience is not a major reason why people with severe eosinophilic asthma, eligible for anti-IL5 treatment, choose not to take existing NICE recommended biologics.* The Committee heard that some people who meet the eligibility criteria for mepolizumab and reslizumab chose to remain on standard of care because of personal preferences and that the convenience of administration offered by benralizumab is potentially very beneficial to patients. Although somewhat limited by sample size, we would like to attempt to put this in context following a recent GSK-market research study. **COMMERICAL IN CONFIDENCE INFORMATION REMOVED**
9	**The manufacturer has not presented clinical and cost-effectiveness evidence to support a broadening of the proposed draft guidance population.** As we have already stated we believe the proposed population on which NICE has issued a draft positive recommendation for benralizumab is a fair reflection of the evidence presented and the appraisal process to date. Benralizumab remains not cost-effective in terms of acceptable ICER thresholds, compared with mepolizumab in the mepolizumab NICE recommended population. The comparison of efficacy is based on a highly uncertain Matching Adjusted Indirect Comparison and we presume that benralizumab has a higher net price compared with mepolizumab. In a scenario where further evidence and / or a revised PAS is provided by the manufacturer, and the final guidance population is broadened to the manufacturer's preferred population (blood eosinophil count of ≥ 300 cells/μL, ≥ 3 exacerbations in the previous 12 months and or on maintenance oral corticosteroids), we seek assurance that the ICER for the sub-population of blood eosinophil count of ≥ 300 cells/μL, ≥3 exacerbations and not on maintenance oral corticosteroids is presented for transparency. To date the ERG have concluded that the ICER is unlikely to fall within acceptable thresholds Further, based on the manufacturer's response to ACD1, observational epidemiology data suggested this population was also larger compared with that included in the benralizumab pivotal trials which therefore calls into question the generalisability of the trials. We have significant concerns that agreeing to a broader population would undermine the value for mepolizumab that GSK has offered to the NHS and patients in England and Wales. In this scenario, we would like to highlight our strong intention to seek a re-appraisal. We strongly refute that the differences in the comparative efficacy seen in the intention to treat populations can and should be applied to more severe sub-groups. Further, the rate ratio of mepolizumab vs. placebo for reduction in exacerbations among patients with blood eosinophils of ≥300 cells/μL at baseline and a history of ≥3 exacerbations in the past year 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). We also believe the economic proposition for mepolizumab would remain strong for the NHS in the case of a re-appraisal.

Insert extra rows as needed

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- 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.
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Benralizumab for treating severe eosinophilic asthma [ID1129]

NICE National Institute for Health and Care Excellence

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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):	N**HS England**
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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	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 proposed treatment population is not clinically relevant for the following reasons: 1. The eosinophil count should be 300. Both phase III pivotals (SIROCCO and CALIMA) used an eosinophil count of 300 for study entry. 2. Pooled analysis of SIROCCO and CALIMA clearly demonstrates that people with eosinophils of 300 or higher and 3 exacerbations in the previous 12 months have an enhanced response (Fitzgerald et al. Lancet Respir Med 2018; 6: 51-64). 3. For people with severe asthma the ability to reduce/remove oral corticosteroids (OCS) is frequently as, or more, important than preventing future attacks. Given the strength of the ZONDA data, the population should include people with 3 or more exacerbations or who are taking continuous OCS. Otherwise it is illogical to have a clinically significant reduction in OCS as one of the definitions of an adequate response at 12 months. OCS use also predicts response to benralizumab (Fitzgerald et al. Lancet Respir Med 2018; 6: 51-64). 4. There have been no clinical trials of benralizumab in people with severe eosinophilic asthma in whom 'mepolizumab is not a treatment option' or have failed a trial of mepolizumab.
2	We are concerned that the committee has misinterpreted the available clinical evidence to come to the conclusion that the 'mixed' population suggested by the company is not suitable for considering the cost effectiveness of benralizumab compared with standard care for the following reasons: 1. This mixed population equates to the mepolizumab and omalizumab HTAs, neither of these HTA are based on trial data suggesting that this is the correct target population. There is stronger evidence that this is the correct population for benralizumab based on the published responder analysis (Fitzgerald et al. Lancet Respir Med 2018; 6: 51-64). 2. The committee are incorrect in their assumption that the company's proposed population include people with different severities of asthma. The whole

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	population falls within the ERS/ATS definition of severe asthma (Chung et al. Eur Respir J 2014; 43: 343-73) and as clinicians we would not differentiate between individual people with severe asthma in the way suggested by the committee. 3. Eosinophil level does not differentiate between asthma severity, the level in an individual person varies significantly in time and with treatment (Newby et al. Plos One 2014). People with mild asthma can have elevated blood eosinophil levels.
3	Should the eosinophil trigger level be standardised for all IL5 inhibitors?
4	There is no logic to the failed mepolizumab threshold. They are alternative drugs.
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6	

Insert extra rows as needed

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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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Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that with the following statement in section 3.13: '**It considered that although the simple assumption of clinical equivalence between the 2 treatments {benralizumab and reslizumab} is questionable, it is reasonable to assume that they are not very different.**' We are not aware of any clinical data directly comparing these two treatments and therefore this assumption is unfounded. In addition we would like to draw to the committee's attention to indirect evidence that indicates a efficacy difference between these 2 treatments: subgroup analysis from the Phase III trials for patients with 3 or more CAEs: 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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Comments on the ACD Received from Experts through the NICE Website

Name	Lehanne Sergison
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on the ACD:

I am concerned that the recommendation will mean that a large number of patients will not meet the criteria of having an eosinophil level over 400. Patients with severe eosinophilia asthma are desperate to lead as full and meaningful lives as possible without the burden the disease and taking ocs. The research has proven that potentially Benralizumab could have life changing benefits to patients with eosinophil levels of 300 and to deny them this opportunity seems most unjust.

I am aware of a number of patients who have been treated with Mepolizumab and have had to stop their treatment because of adverse effects or no improvement. Some of these patients do not meet the criteria of Reslizumab and will not meet the guidance for Benralizumab. From a patient's perspective, it seems most unreasonable that despite the research demonstrating that Benralizumab can make significant improvements to patients with an eosinophil level of over 300 NICE has made a recommendation that will deny this group of patients access to a potentially life changing treatment.

In making their recommendation, I am concerned that the panel has not put sufficient weight on the benefit of administering Benralizumab every eight weeks as opposed to four weekly with Mepolizumab, and more importantly the added benefit that it may be self administered. This is a huge benefit to patients. Many patient have to travel long distances to specialist centres for Mepolizumab or Reslizumab and may have to take a day off work, arrange child care etc and there is also the financial cost to consider. Patients with chronic condition are constantly fearful of losing their jobs due to a poor sickness records and taking time off work for appointments etc. Furthermore, the impact of long term ocs use many of these patients may have co-morbidities and potentially may be under the care of a number of hospital consultants thereby juggling lots of hospital appointments. Self administration of be Benralizumab would be huge step forward for patients and would surely free up a significant amount of time in specialist centres.

The recommendation does not give any consideration to patients who are on permanent ocs to manage their condition who may not have asthma exacerbation as such but may benefit from Benralizumab. Prednisolone is dreadful drug to take, which can cause a multitude of side effects, Benralizumab is potentially steroid sparing and should be considered as an option for these patients.

Name	Dr Samantha Walker
Role	Director of Research and Policy
Other role	Asthma UK, research and patient charity
Organisation	Asthma UK
Location	England
Conflict	No
Notes	

Comments on the ACD:

Severe asthma patients have a significant unmet need for more and better treatments

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 200,000 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 a disproportionate number of the people that die from asthma have severe asthma (40% of those who died).

The severe asthma patient group is one with a significant unmet need. Current oral corticosteroid (OCS) treatments often result in unpleasant side effects such as sleep disturbance and increased appetite and long-term co-morbidities such as diabetes and osteoporosis. As new Asthma UK research shows, there is significant disparity in referral criteria and rates for severe asthma, stopping many patients from accessing specialised care (Asthma UK, Slipping through the net, 2018, https://www.asthma.org.uk/get-involved/campaigns/publications/difficult-and-severe-asthma-report/).

New monoclonal antibody treatments are welcomed, but are still difficult to access

New monoclonal antibody treatments such as benralizumab offer a welcome alternative treatment option for those with severe asthma. However, referral rates to severe asthma centres and prescriptions for these new treatments are low and variable. This may be because non-steroid-based treatments for severe asthma are still relatively new and many healthcare professionals may not know if their patients could benefit from the new treatment options.

Although existing biologics have offered relief of symptoms to some, they are limited in that they are only made available to a specific sub-population (e.g. people with eosinophil count of 400 and three or four exacerbations per year), and not all monoclonal antibody treatments work for each individual patient. As such, the approval of a new biologic offers an opportunity to help more people with severe asthma.

On behalf of people with severe asthma, Asthma UK aims to improve access to specialised services and to make new treatments available to all who could benefit. Asthma UK would also like to see further research into monoclonal antibodies to promote more targeted prescribing, improving patient outcomes and reducing the prescription of ineffective treatments.

The eligibility criteria for benralizumab are too restrictive and may mean people miss out on life changing treatments

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 welcomes NICE's decision to approve its use on the NHS in England.

However, Asthma UK is concerned that the guidance only approves the use of benralizumab for patients with an eosinophil count of over 400 and three exacerbations within the past year, even though there is evidence that benralizumab may be effective for a wider population.

Patients with an eosinophil count of 300-399 and 3 exacerbations in 12 months are currently not eligible for other monoclonal antibodies available, and their only treatment option is OCS which cause significant adverse side effects. We are concerned that the restrictions on eligibility to benralizumab mean many people will continue to miss out on life changing treatments and remain on damaging OCS treatments indefinitely. As one severe asthma clinician told us in our recent report, these patients on long term OCS often miss out on specialised care and new treatments: The problem is long-term damage done by steroids by the time they get to us. Also, once they are stable on steroids, they kind of slip through the net, their hospital admissions reduce, so they're not flagged up as often.
As well as lowering the eosinophil threshold, Asthma UK would like to see continuous OCS use as another criterion for eligibility for benralizumab (and other monoclonal antibodies). Patients on OCS may appear ineligible for benralizumab because eosinophil levels are reduced by OCS and OCS also suppress asthma attacks. A lower eosinophil count does not necessarily mean that a patient''s asthma is less severe and they should still be eligible for benralizumab.

The guidance is too restrictive over when benralizumab can be prescribed over another monoclonal antibody
Additionally, Asthma UK is concerned at the guidance's stipulation that for eligible patients, mepolizumab should be tried before benralizumab. It is not practical from a patient's perspective to switch from another biologic to benralizumab. In order to meet the eligibility criteria as specified in the draft guidance, there would have to be a significant period between treatments, and off any eosinophil-suppressing treatments, during which time the patient's asthma is at risk of deteriorating, putting them at serious and unacceptable risk of exacerbations.
Benralizumab may be more favourable to a patient for reducing the burden of managing severe asthma, as it requires less frequent dosing and in the method of administration. This is particularly important in light of patients travelling long distances and taking time off work to visit specialist clinics. Patient choice and wellbeing should be an important factor in which monoclonal antibody should be prescribed by clinicians. In determining which monoclonal antibody to prescribe, suitability and preference for each patient should be considered, and the guidance should not promote one treatment over another.

Recommendations from Asthma UK on the second appraisal of benralizumab for treating severe eosinophilic asthma:

- Asthma UK calls for NICE to approve benralizumab as a treatment for the wider population for whom it is clinically effective and for whom there are no alternative new treatments (patients with 300+ eosinophil count and at least three exacerbations in the past year)
- Asthma UK calls for NICE to approve benralizumab as a treatment for patients with severe asthma who are already receiving continuous OCS treatment
- Asthma UK calls for NICE to remove the requirement that mepolizumab should be tried before benralizumab
- Asthma UK calls for NICE and AstraZeneca to reach agreements on price and cost effectiveness to extend eligibility of the treatment to the maximum number of potential patients who could benefit

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

Name	[redacted]
Role	Profressor of allergy and pulmonology
Other role	NHS Professional
Organisation	[redacted]
Location	Scotland
Conflict	No
Notes	
Comments on the ACD:	
I feel the NICE guidance will be detrimental to my patients with severe eosinophlic asthma if as suggsted I have to first show that they fail on mepolizumab as standard of care . Aside from any cost issues I feel it is important to have to the option of different biologics even within the same class ,bearing in mind that benralizumab works via a different receptor mediated mechanism of depleting eosinophils .At present our response rate to Mepolizumab as unit is running at around 30% in highly selected patients who have been evaluated in an MDT setting .Hence having only one default anti-IL5 is surely going to have an adverse impact on patient care .Moreover I don't see the logic in setting a blood eosinophil cut off of 400/ul along with an exacerbation history of at least 4 in the past year as this will markedly limit the number of eligable patients who could recieve benralizumab . All of this along with a more patient friendly dosing regimen every 8 weeks for benralizumab (after the first 3 doses) would mean my patients would be missing out of an alternative highly effective option . Bear in mind by the time patients have failed on Mepolizumab they are then a further 12 months down the line and have been exposed to the cumulative systemic adverse effect burden of another 4-8 weeks of oral corticosteroid . As someone who has been exposed to oral corticosteroids as a patient I find this unacceptable .	

Name	[redacted]
Role	Consultant Respiratory Physician
Other role	NHS Professional
Organisation	[redacted]
Location	England
Conflict	Yes – not specified
Notes	

Comments on the ACD:

1. General

As clinicians looking after people with severe asthma in the UK, we would like to comment on the NICE appraisal consultation document on Benralizumab for treating severe eosinophilic asthma. We are pleased that multiple novel therapies have been proven to be both clinically and cost effective and for some people with severe asthma these options have been transformative. However, there is a clear need for additional therapeutic options.

We strongly disagree with the draft recommendation that benralizumab is recommended for a narrow population of people with blood eosinophils of 400 or more with at least 3 exacerbations in the last 12 months in whom mepolizumab is not an option.

The summaries of clinical effectiveness used to generate this patient group suggested in the ACD are not reasonable interpretations of the evidence. We feel that the current provisional recommendations are not sound and are not a suitable basis for guidance to the NHS.

As the clinical leads for severe asthma care across England we do not think that the committee has correctly interpreted the evidence to produce a logical summary of the clinical effectiveness. We strongly support the company's proposed population from a clinical perspective and urge NICE and Astra Zeneca to have further discussions with regards the Patient Access Scheme to allow clinicians to treat the correct patient cohort and people with severe asthma to receive the care that they need.

The following consultant respiratory physicians have been involved in producing this document and endorse its findings:
Dr Andrew Menzies-Gow, Royal Brompton Hospital.
Professor Ian Pavord, University of Oxford
Dr Dave Allen, Wythenshawe Hospital
Dr Adel Mansur, Birmingham Heartlands Hospital
Professor Salman Siddiqui, Glenfield Hospital
Professor Dominick Shaw, Nottingham University Hospitals NHS Trust
Dr David Jackson, Kingâ's Health Partners
Dr Paul Pfeffer, Bartâ's Healthcare
Dr Robin Gore, Addenbrookes Hospital
Professor Anoop Chauhan, Portsmouth Hospital
Professor Ian Sabroe, University of Sheffield
Dr Ian Clifton, Leeds Teaching Hospital NHS Trust
Dr Matthew Masoli, Derriford Hospital
Dr Paddy Dennison, Southampton University Hospital

2. Section 1.1

Proposed Treatment population

This population is not clinically relevant and has been produced due to a fundamental lack of understanding of severe eosinophilic asthma. As the clinical leads for severe asthma at nationally commissioned centres we agree with the company's proposed

population for the following reasons:

1. The eosinophil count should be 300. Both phase III pivotals (SIROCCO and CALIMA) used an eosinophil count of 300 for study entry.
2. Pooled analysis of SIROCCO and CALIMA clearly demonstrates that people with eosinophils of 300 or higher and 3 exacerbations in the previous 12 months have an enhanced response (Fitzgerald et al. Lancet Respir Med 2018; 6: 51-64).
3. For people with severe asthma the ability to reduce/remove oral corticosteroids (OCS) is frequently as, or more, important than preventing future attacks. Given the strength of the ZONDA data, the population should include people with 3 or more exacerbations or who are taking continuous OCS. Otherwise it is illogical to have a clinically significant reduction in OCS as one of the definitions of an adequate response at 12 months. OCS use also predicts response to benralizumab (Fitzgerald et al. Lancet Respir Med 2018; 6: 51-64).
4. There have been no clinical trials of benralizumab in people with severe eosinophilic asthma in whom mepolizumab is not a treatment option or have failed a trial of mepolizumab.
5. As clinicians we do not understand what is meant by 'mepolizumab is not a treatment option'? The HTA for mepolizumab suggests treating for 12 months, it will be impossible to switch to benralizumab at that point as there is a requirement for an eosinophil count of 400 or higher in the last 12 months and in all cases mepolizumab will have suppressed the eosinophil count over that time period and potentially for several months following cessation of mepolizumab (Haldar et al. J Allergy Clin Immunol 2014; 133: 921-3). Are the committee suggesting that following an unsuccessful trial of mepolizumab people with severe asthma should have to continue with OCS and all their concomitant side effects until the eosinophil count recovers?

3. <u>Pages 4-5</u>

Why the committee made these recommendations

We fundamentally disagree with the statement that the mixed population suggested by the company is not suitable for considering the cost effectiveness of benralizumab compared with standard care for the following reasons:

1. This mixed population equates to the mepolizumab and omalizumab HTAs, neither of these HTA are based on trial data suggesting that this is the correct target population. There is stronger evidence that this is the correct population for benralizumab based on the published responder analysis (Fitzgerald et al. Lancet Respir Med 2018; 6: 51-64).
2. The committee are incorrect in their assumption that the company's proposed population includes people with different severities of asthma. The whole population falls within the ERS/ATS definition of severe asthma (Chung et al. Eur Respir J 2014; 43: 343-73) and as clinicians we would not differentiate between individual people with severe asthma in the way suggested by the committee.
3. Eosinophil level does not differentiate between asthma severity, the level in an individual person varies significantly over time and with treatment (Newby et al. Plos One 2014). People with mild asthma can have elevated blood eosinophil levels.

4. <u>Section 3.3</u>

3.3 Please update to the GINA 2018 guidelines, which include benralizumab as a treatment option.

Benralizumab for severe asthma:

NICE STA

Response:

Between 2nd and 3rd NICE Appraisal Committee meetings

7th September, 2018

Response to comments from Lehanne Sergison

The ERG agree that the available clinical evidence demonstrates effectiveness at 300 cells/μL eosinophil count. Therefore, the recommendation to restrict to 400 cells/μL eosinophil count is not in keeping with the clinical evidence.

Response to comments from Association of Respiratory Nurse Specialists

The ERG believe it is incorrect to say that SIROCCO and CALIMA used eosinophil count of 300 cells/μL as a study entry criterion. However, the ERG agree that the subgroup analysis on which the company's submission was based (where patients with eosinophils less than 300 cells/μL were excluded) provided sufficient evidence for clinical effectiveness.

Response to comments from NHS England

- The ERG agree that OCS use predicted response to benralizumab (Fitzgerald et al. Lancet Respir Med 2018; 6: 51-64).
- The ERG agree that the ZONDA data do show the benefit of OCS reduction.
- The ERG's clinical advisor, Prof. David Halpin, agrees with the suggestion that all patients in the company's proposed population fit the definition of severe asthma appears sound, in light of ERS/ATS definition of severe asthma (Chung et al, 2014).

Response to comments from AZ

The ERG agree that the clinical evidence does support a broader population than the ACD recommendation.

Response to comments from GSK

- GSK propose benralizumab only being for those who are ineligible for mepolizumab – the ERG do not agree that the clinical evidence supports narrowing the population in this way.
- The ERG disagree with GSK that the narrowed population suggested in the ACD is reflective of the clinical evidence.

Response to web comment from [redacted]

- The ERG agree that there have been no trials of benralizumab in people with severe eosinophilic asthma in whom mepolizumab is not a treatment option or have failed a trial of mepolizumab. The ERG have identified an ongoing trial (ClinicalTrials.gov Identifier: NCT03470311) due for completion by June 2019. The trial is investigating efficacy of benralizumab in patients who remained uncontrolled despite previous treatment with 100 mg mepolizumab administered subcutaneously Q4W or reslizumab 3 mg/kg IV Q4W for at least 6 months.
- The ERG's clinical advisor agrees that it is reasonable to suggest that it will be impossible to switch to benralizumab after failing on mepolizumab as there is a requirement for an eosinophil count of 400 or higher in the last 12 months and the eosinophil count will be low in patients treated with mepolizumab.

- Prof. Halpin also agrees on the view that eosinophil level does not differentiate between asthma severity, and that people with mild asthma can have elevated blood eosinophil levels.

Response to web comment from [redacted]

The ERG's clinical advisor agrees with [redacted] that the whole population falls within the ERS/ATS definition of severe asthma.

Response to comments from BTS

The ERG's clinical advisor agrees that many of the patients who stand to benefit most from benralizumab will have eosinophil counts suppressed by oral steroids.

Response to comments from Teva

The ERG agree that equivalent efficacy was assumed for benralizumab and reslizumab in exacerbation reductions and ACQ transitions without evidence to support it.

Benralizumab for severe asthma:

NICE STA

Addendum:

Between 2nd and 3rd NICE Appraisal Committee meetings

Additional analyses conducted by the ERG for the comparison versus standard of care assuming a revised PAS price for benralizumab

13th September, 2018

Information that is commercial-in-confidence is [redacted].

1 Cost effectiveness of benralizumab vs. standard of care in patients with eosinophil count of 300-399 cells/µL, 3 severe exacerbations in the prior year, and no maintenance oral corticosteroids use at baseline

The company provided cost-effectiveness results for benralizumab (BEN) vs. standard of care (SoC) for the patient population with eosinophil count (EOS) of 300-399 cells/µL, exactly 3 exacerbations in the prior year, and no maintenance oral corticosteroids (mOCS) use at baseline (which the company referred to as the *non-biologic eligible population*). The revised PAS price for benralizumab was [redacted] per 30 mg subcutaneous injection.

The company provided the following (updated) parameter values:

- health state transition probabilities, estimated from a pooled SIROCCO and CALIMA data set for the *non-biologic eligible population* (300-399 EOS, 3 exacerbations, and no mOCS use), treated with:
    - BEN:
        - Transition probabilities for weeks 0-52 (Table 9, company's response)
        - Transition probabilities for weeks >52 (Table 10, company's response)
    - SoC: a set of probabilities for all weeks (Table 11, company's response)
- health state utilities (Table 12, company's response)

The company also presented the rate ratio for marginal annual exacerbations of 0.39 from a pooled SIROCCO and CALIMA subgroup analysis for the *non-biologic eligible population* (Table 1). The p-value was 0.178 indicating that the result was not statistically significant

Table 1: Efficacy in the pooled SIROCCO and CALIMA subgroup analysis of patients with blood eosinophil level ≥300 cells/µL and exactly 3 exacerbations

Estimate, 95% CI	Benralizumab 30mg Q8W (N=16)	Placebo (N=14)
Marginal annual exacerbation rate	0.51 (0.15,1.46)	1.26 (0.54,2.74)
Rate ratio	0.39 (0.10,1.54)	
P value	0.178	

Source: Table 8, company's comments

All other parameter in this analysis were the same as for the base-case population. In particular, the company assumed that:

1. the proportions of patients responding to benralizumab (at 52 weeks) in the *non-biologic eligible population* (300-399 EOS, 3 exacerbations, and no mOCS use at baseline) is the same as in the base-case population (300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS);

2. the distribution of exacerbations (i.e. proportions of OCS treated exacerbations, exacerbations treated in the emergency department, and those requiring hospitalisation) is also the same in these two populations.

The ERG believe, however, that the hospitalisation rate is likely to be lower in the *non-biologic eligible population* when compared with the base-case population. Of note, hospitalisation for severe exacerbations was modelled only in patients treated with SoC while no patients on BEN were assumed to experience severe exacerbations requiring hospitalisation. Therefore, the assumption on the same hospitalisation rate as in the base-case population improves the cost-effectiveness of BEN in the *non-biologic eligible population.*

The ERG believe that the results of the cost-effectiveness analysis conducted by the company for the *non-biologic eligible population* is highly uncertain for the following reasons:

- a very small sample used to obtain the updated transition probabilities
- an inconsistency between the updated exacerbation rate ratio (Table 1) and the results of the pooled SIROCCO and CALIMA analysis (refer to Table 2 and Figure 1 reproduced from FitzGerald et al., 2017)

Parameterisation of the (four-by-four) health state transition matrices using a small data set of 16 and 14 patients on BEN and placebo, respectively (see Table 1), with about one exacerbation per patient per year (Table 17, SIROCCO CSR), entail high uncertainty. Furthermore, the rate ratio of 0.39 for the *non-biologic eligible population* is likely an underestimate. As shown in Table 2, the RR for the patient population with (exactly) 2 exacerbations was 0.73, and 0.45 for patients with ≥3 exacerbations. Therefore, the RR for patients with (exactly) 3 exacerbations is likely to lie between those two numbers.

In addition to reporting RR estimates stratified by the number of exacerbations in the prior year, FitzGerald et al. (2017) modelled the dependence of annual exacerbation rate on baseline EOS (Figure 1). It is clearly seen from the figure that the rate ratio of exacerbations is higher for lower EOS at baseline.

Based on this, the rate ratio of 0.47 (reported in the company's submission for pooled SIROCCO and CALIMA) could be considered *the lower bound* for the RR in the population with 300-399 EOS, 3 exacerbations, and no mOCS use at baseline. Therefore, the ERG believe that employing the transition probabilities used for the base-case population would be more appropriate.

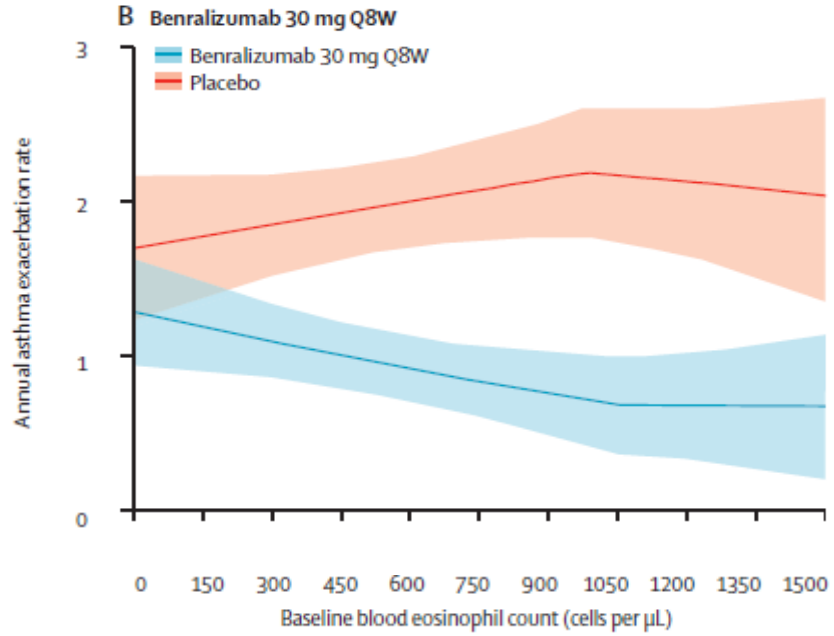
It should be noted here that the rate ratio of 0.39 indicating a lower risk of exacerbations in BEN when compared with SoC would improve the cost effectiveness of BEN.

Table 2: Association of exacerbation history with effect of benralizumab treatment on efficacy variables for patients with baseline eosinophil counts ≥300 cells/μL (full analysis set, pooled)

[redacted]

CI, confidence interval; Q8W, every 8 weeks (first three doses every 4 weeks)
Source: Table 6, FitzGerald et al. (2017)

Figure 1: Modelling of asthma exacerbation rate by baseline blood eosinophil counts for patients with baseline history of ≥3 exacerbations in the year before treatment



Asthma exacerbation rate for benralizumab Q8W in the pooled analysis set. Lines show locally weighted smoothing local regression plot and shading shows 95% CI.
Q8W=every 8 weeks (first three doses every 4 weeks).
Source: Figure 4, FitzGerald et al. (2017)

Under the updated utility values (see Table 12, company's response), the same transition probabilities as for the base-case population, and all other assumptions as in the ERG's base case, the ICER for the *non-biologic eligible population* (300-399 EOS, 3 exacerbations and no mOCS use at baseline) is £45,406 per quality-adjusted life year (QALY) gained (Table 4). Importantly, this estimate represents *the lower bound* for incremental cost-effectiveness ratio in the BEN vs. SoC comparison in this particular population. To be cost-effective at the threshold of £30,000 per QALY, the price for BEN should be under [redacted] per vial, and no more than [redacted] per vial at the threshold of £20,000 per QALY gained (Table 4).

Table 3: Cost-effectiveness results for BEN vs. SoC in patients with 300-399 EOS, exactly 3 exacerbations and no mOCS use at baseline

Technology	Total discounted costs (£)	Total discounted QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£45,406
SoC	[redacted]	[redacted]	-	-	-

BEN, benralizumab; EOS, eosinophil count; mOCS, maintenance oral corticosteroids; QALY, quality-adjusted life year; SoC, standard of care

Table 4: Threshold analysis for BEN vs. SoC in patients with 300-399 EOS, exactly 3 exacerbations and no mOCS use at baseline

ICER threshold, £ per QALY gained	Discount for BEN[1], %	BEN price, £
£30,000	[redacted]	[redacted]
£25,000	[redacted]	[redacted]
£20,000	[redacted]	[redacted]

[1] Discount applied to the BEN price of [redacted]. BEN, benralizumab; EOS, eosinophil count; mOCS, maintenance oral corticosteroids; QALY, quality-adjusted life year; SoC, standard of care

2 Cost effectiveness of BEN vs. SoC in patients from the base-case population

2.1 Percentage of patients on mOCS at baseline for the BEN vs. SoC comparison in the base-case population

The ERG thank AstraZeneca for finally providing raw data (Table 2, company's comments) from a company-sponsored study, which the company referred to in their submission to NICE. Based on this data, the estimate of 54.1% appears accurate.

2.2 Cost-effectiveness results for BEN vs. SoC comparison in the base-case population

Assuming that 54.1% of patients in the base-case population are taking mOCS at baseline, and the revised BEN price of [redacted] per vial (with all other assumptions as in the ERG's base case), the ICER for the comparison of BEN vs. SoC is £25,587 per QALY gained (Table 5).

Table 5: Cost-effectiveness results for BEN vs. SoC in patients from the base-case population with 54.1% of patients on mOCS at baseline

Technology	Total discounted costs (£)	Total discounted QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
Add-on benralizumab	[redacted]	[redacted]	[redacted]	[redacted]	£25,587
SoC	[redacted]	[redacted]	-	-	-

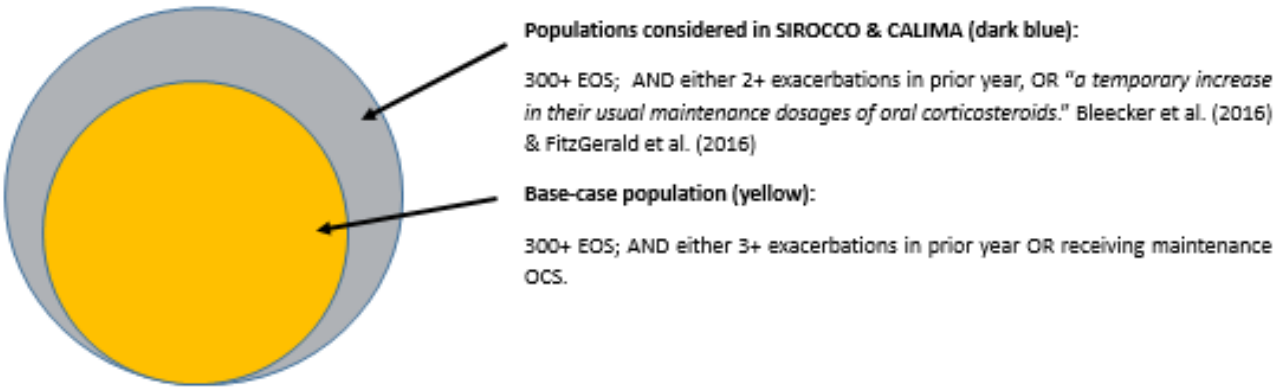
BEN, benralizumab; mOCS, maintenance oral corticosteroids; QALY, quality-adjusted life year; SoC, standard of care

3 Generalisability to the NHS in England

The company stated in their response: "It should be noted that the percentage of patients with exactly 3 exacerbations (and not on mOCS) according to RWE presented by the company (31.2%) is given as a percentage of the entire base case population where a recommendation is sought i.e. those patients with 300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS. *The percentages of patients presented by the ERG (19.9% for both arms in SIROCCO and 24.7% and 22.6% for Q8W and placebo arms in CALIMA) are taken from the SIROCCO and CALIMA trial CSRs and are therefore given as a percentage of the entire trial primary end point populations (i.e. those patients with 300+ EOS; AND 2+ exacerbations in prior year) and not as a percentage of the base case population. Clearly these patient populations are not equivalent*."

The ERG agree with the statement shown above in *italic*. However, the ERG believes that those estimates (19.9% for both arms in SIROCCO and 24.7% and 22.6% for Q8W and placebo arms in CALIMA) could be considered as upper bounds for the size of the base-case population (300+ EOS; AND either 3+ exacerbations in prior year OR receiving maintenance OCS), because, as it was rightly pointed out by the company, the proportions reported in the CSRs also include patients with 2 exacerbations in the previous year (a schematic representation of the populations from SIROCCO and CALIMA, and the base-case population is shown in Figure 2). Those were the best estimates available to the ERG (which could serve as reference points) since the *ERG did not have access to individual patient data because the company refused to provide it.*

Figure 2: Patient populations from SIROCCO and CALIMA vs. the base-case population



As stated in Bleecker et al. (2016), the inclusion criteria in the SIROCCO trial were "at least two documented asthma exacerbations needing systemic corticosteroid treatment *or a temporary increase in their usual maintenance dosages of oral corticosteroids* within 1 year before enrolment."
In CALIMA (FitzGerald et al., 2016), patients must have had "two or more asthma exacerbations in the 12 months before enrolment that required use of a systemic corticosteroid *or temporary increase in the patient's usual maintenance dosage of oral corticosteroids*."

As for the trial-based estimate of 7.3% for the size of the *non-biologic eligible population* (300-399 EOS, 3 exacerbations, and no mOCS use at baseline) (Table 1, company's response), it appears accurate.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Benralizumab for treating inadequately controlled asthma

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Adel Mansur**
2. Name of organisation	**University Hospitals of Birmingham**

3. Job title or position	**Consultant physician and honorary reader**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes
The aim of treatment for this condition	

7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce exacerbation, improve disease control and improve quality of life and reduce exposure to corticosteroids.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in number of steroids require exacerbation and reducing or weaning off maintenance corticosteroids treatment
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, still significant number of patients suffer from severe disease with no currently available treatment options
What is the expected place of the technology in current practice?	
10. How is the condition	Patients with severe asthma are treated in standard way as per national and international guidelines. A subgroup of this population such as severe allergic asthma can be treated with omalizumab, other

currently treated in the NHS?	technologies available is mepolizumab, reslizumab for severe eosinophilic asthma and bronchial thermoplasty.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes BTS/SIGN and NICE asthma guidelines in UK
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is differences in asthma management e.g. NICE and BTS/SIGN guidelines differ in some aspects. However the guidelines at the level of severe asthma generally agree and uses NICE recommendations.
• What impact would the technology have on the current pathway of care?	Benralizumab will add another option for the treatment of patients with eosinophilic asthma that currently have corticosteroids as mainstay of treatment with accompanying significant side effects and poor QoL.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Will be used in a similar way to other available biologicals with potential differences
• How does healthcare resource use differ	Benralizumab will be administered every two months instead of monthly dosing that is required for other

between the technology and current care?	anti-IL5 such as mepolizumab.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Tertiary centres in severe asthma
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training of severe asthma teams to administer the treatment and monitoring of response
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes it is expected to improve asthma control, reduce exacerbations and exposure to steroids.
• Do you expect the technology to increase length of life more than current care?	Yes in the sense that severe asthma patient life expectancy is shorter than average population due to disease severity and comorbidities resulting from the disease and its treatment with excessive corticosteroids. Improving disease control and reducing exposure to corticosteroids would improve survival expectency.
• Do you expect the technology to increase health-related quality of	Yes

life more than current care?	
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	People with severe eosinophilic asthma would benefit from this technology. The evidence here shows benefit in the group with at least 300cells/mcl of blood eosinophil level and at least 3 exacerbations requiring steroids in the last 12 months or those on maintenance corticosteroids.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional	Probably would be easier, as it is ready made injections and does not require preparation to administer. Other factors are similar to existing ones with biological treatments, however the frequency of the treatment will be less.

tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, patients fitting the set criteria will be administered the treatment every two months for 12 months with aim of reducing steroids dose by 50% or exacerbations by 50%.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes will provide another treatment options for those with severe disease that currently require steroids treatment. It will help to improve patients QoL, less steroids and less severe exacerbations that may lead to hospitalisation and excessive use of health care resources

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes and will provide another option with extended population compared to other anti-IL5 options
• Does the use of the technology address any particular unmet need of the patient population?	yes
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Generally clinical trials showed good safety profile with no significant side effects.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Exacerbations reduction and reducing maintenance steroids requirement and yes being showing in clinical trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Similar outcomes to those being used in clinical trials will be used in clinical practice
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None that I am aware of
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator	Yes one published paper in JACI

treatment(s) since the publication of NICE technology appraisal guidance 431 (mepolizumab) and NICE technology appraisal guidance 479 (reslizumab)?	
22. How do data on real-world experience compare with the trial data?	I am not aware of real-world data at the moment
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	None that I am aware off
23b. Consider whether these issues are different from issues with current care and why.	As above

Topic-specific questions	
24. Is diagnosis, disease progression and treatment pathway for severe eosinophilic asthma likely to differ between adolescents from age 12 upwards and adults? 25. Is it reasonable to assume clinical equivalency between reslizumab and benralizumab, considering they have different mechanism of action? Is the company's assumption that all clinical values and therefore transition probabilities are equivalent appropriate? 27. Is it reasonable to assume (in the absence of data) that	Generally no, however during the teenage period some patients disease reduce in severity.

the relative efficacy between an overall population and the more severe sub-group would be equal for benralizumab and mepolizumab? Yes	

Key messages

28. In up to 5 bullet points, please summarise the key messages of your statement.

- Benralizumab is effective in treatment of eosinophilic severe asthma
- It has comparable efficacy to other available anti IL5 biological treatment
- Evidence show the target population should include those on maintenance steroids, blood eosinophils of 300 and exacerbations of 3 or more.
- Should be available as first line for biological treatment
- The two monthly frequency of administration carry an advantage over other two available similar products

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.