National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Benralizumab for treating severe asthma

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	AstraZeneca	Yes. It is appropriate to refer this topic to NICE; and we consider the Single Technology Appraisal (STA) process to be appropriate for this appraisal. Benralizumab will provide a highly significant health benefit to patients with severe eosinophilic asthma. In the regulatory trials (Bleecker, 2016; FitzGerald, 2016; DOF BEN-020-APR2017), benralizumab compared to placebo, when both are added on top of their background therapy (medium/high dose ICS plus LABA ± OCS ± controller). • reduces the annual asthma exacerbations rate • reduces the rate of exacerbations associated with hospitalization/A & E visits • improves lung function • [redacted]	Thank you for your comment.

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		• reduces asthma symptoms; improves asthma control, and asthma-associated QoL References Bleecker ER, et al. The Lancet. 2016 4;388(10056):2115-27. FitzGerald J, et al. The Lancet 2016 4;388(10056): 2128-41. Data on File, BEN-020-APR2017	
	BSACI	Yes although presumably consideration needs to await marketing authorisation	Thank you for your comment.
	British Thoracic Society	This topic is relevant and addresses priority issues for severe asthma patients who have few options for improving quality of life and other markers. Up until recently there has been only one biologic agent available to treat severe asthma and patients have had to rely on long term systemic steroids with the accompanying adverse effects. These treatments are costly and it is appropriate that they are evaluated accordingly.	Thank you for your comment.
	Royal College of Physicians (RCP)	Certainly appropriate for this type of severe asthma.	Thank you for your comment.
	Teva UK Limited	No comment	Thank you.
Wording	AstraZeneca	To more closely reflect the expected indication of benralizumab (please see regulatory section below), we suggest that the remit is changed to:	Thank you for your comment. The remit has been amended to “To appraise the clinical and cost effectiveness of benralizumab within its

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		"To appraise the clinical and cost effectiveness of benralizumab within its marketing authorisation for treating severe asthma with an eosinophilic phenotype".	marketing authorisation for treating severe asthma with elevated blood eosinophils." The committee will only be able to make recommendations in line with the marketing authorisation for benralizumab.
	BSACI	I wouldn't be so specific about blood eosinophils in the wording. I would suggest instead 'inadequately controlled severe eosinophilic asthma'	Thank you for your comment. The remit has been amended to "To appraise the clinical and cost effectiveness of benralizumab within its marketing authorisation for treating severe asthma with elevated blood eosinophils." This is in line with scopes for other related NICE technology appraisals. The committee will only be able to make recommendations in line with the marketing authorisation for benralizumab.
	British Thoracic Society	Yes.	Thank you for your comment.
	Royal College of Physicians (RCP)	Yes appropriate with changes mentioned under Background and technology	Thank you for your comment.

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	Teva UK Limited	No comment	Thank you.
Timing Issues	AstraZeneca	We consider this appraisal to be urgent for the following reasons: 1. As described above, benralizumab will provide substantial health benefits to relevant patients. 2. Subject to final EMA license, benralizumab will offer patients and the NHS, an anti-eosinophilic treatment with a different posology, [redacted] This may be associated with a reduction in the number of product administration visits and associated administration costs; and may give opportunities for care closer to home. We welcome the opportunity to discuss the timelines for this appraisal. If possible, we suggest a manufacturer submission in December 2017/January 2018 ([redacted].)	Thank you for your comment.
	BSACI	This will be a timely appraisal considering that mepolizumab has recently been authorised and reslizumab is being considered	Thank you for your comment.
	British Thoracic Society	Severe asthma remains a significant problem with some commentaries estimating that 50% of the healthcare budget for asthma accounts for 5% of the most severe disease. These patients are those that would gain most benefit from this medication. It is urgent that these medications are evaluated and made available in a timely manner,	Thank you for your comment.
	Teva UK Limited	No comment	Thank you.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	There are key inaccuracies regarding the intervention, which need to be corrected, as described below.	Thank you for your comment. 'The technology' section has been amended to refer to benralizumab as "…a monoclonal antibody against anti-interleukin-5 receptor alpha"
	BSACI	Accurate and appropriate	Thank you for your comment.
	British Thoracic Society	The background wording is not correct. Benralizumab is an antibody to the IL-5 receptor alpha chain which activates antibody dependent cell killing (ADCC) and therefore depletes eosinophils and basophils. It is not an anti-IL-5 so it is different from mepolizumab and reslizumab.	Thank you for your comment. 'The technology' section has been amended to refer to benralizumab as "…a monoclonal antibody against anti-interleukin-5 receptor alpha"
	Royal College of Physicians (RCP)	Further detail required on background pathogenesis of asthma and where benralizumab fits into the heterogeneity of asthma. Benralizumab is a new class of drug acting through a specific anti-inflammatory pathway and thence treats a very specific and important aspect of asthma outcomes namely severe exacerbations. Patient selection is critical to a successful outcome with the drug and as with TA431 there should be extensive discussion about which patients are likely to benefit and how this should be measured Benralizumab is not strictly an anti-IL5 monoclonal rather an IL-5 receptor antagonist.	Thank you for your comment. 'The technology' section has been amended to refer to benralizumab as "…a monoclonal antibody against anti-interleukin-5 receptor alpha"
	Teva UK Limited	No comment	Thank you.

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The technology/ intervention	AstraZeneca	No. The first paragraph of the 'technology' section in the draft scope should be replaced with: "Benralizumab (brand name unknown, Astra Zeneca) is a monoclonal antibody against interleukin-5 receptor α that induces a direct, rapid, and nearly complete depletion of eosinophils, in the bone marrow, blood, and target tissue via enhanced antibody-dependent cell-mediated cytotoxicity. (Bleecker 2016) [redacted] Reference Bleecker ER, et al. The Lancet. 2016 4;388(10056):2115-27.	Thank you for your comment. 'The technology' section has been amended to refer to benralizumab as "…a monoclonal antibody against anti-interleukin-5 receptor alpha"
	BSACI	Yes	Thank you for your comment.
	British Thoracic Society	Yes	Thank you for your comment.
	Royal College of Physicians (RCP)	Not administered IV rather SC. Mepolizumab is now licensed for the same indication but is administered monthly. Benralizumab is administered every second month and has a slightly different mode of action which may have advantages. Therefore important to consider this an important step forward for this group of patients.	Thank you for your comment. 'The technology' section now refers to subcutaneous injection.
	Teva UK Limited	No comment	Thank you.
Population	AstraZeneca	The population should be restricted to adults only as it is expected that benralizumab will receive a license for adult patients only.	Thank you for your comment. The population section has been amended to refer to adults only.

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		To more closely reflect the expected indication of benralizumab (please see regulatory section below), the population should be changed to: “Adults with severe asthma with an eosinophilic phenotype”. It should be noted that the key regulatory exacerbation trials (CALIMA; and SIROCCO) included a minority of patients, who were less than 18 years old with the percentage of patients aged 12-18 years old being 6% or less in each treatment arm. (Bleecker 2016; FitzGerald 2016) We suggest that the following patient sub-groups are considered: • Patients requiring maintenance OCS treatment; • Patients requiring frequent OCS <u>References</u> Bleecker ER, et al. The Lancet. 2016 4;388(10056):2115-27. FitzGerald J, et al. The Lancet 2016 4;388(10056): 2128-41.	
	BSACI	Also need to include patients on maintenance oral corticosteroids	Thank you for your comment. The population has been changed to refer to “adults with severe asthma with elevated blood eosinophils”. This wording reflects the population included in the various trials for benralizumab.
	British Thoracic Society	Yes	Thank you.

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	Royal College of Physicians (RCP)	The patient population contains patients with too mild disease for this drug. It should be similar to the population recommended for mepolizumab ie eosinophilic asthma with frequent exacerbations and those on long term corticosteroids for asthma.	Thank you for your comment. The population currently reflects the population included in the various clinical trials for benralizumab.
	Teva UK Limited	It should be noted that the inclusion criteria and the population studied in the benralizumab Phase III clinical trials was more restrictive than described in the current scope. “We recruited patients (aged 12–75 years) with a physician-based diagnosis of asthma for at least 1 year and at least two exacerbations while on high-dosage inhaled corticosteroids and long-acting β2-agonists (ICS plus LABA) in the previous year.” (CALIMA & SIROCCO studies). We believe that the phase III benralizumab population studied should be more clearly reflected in the population	Thank you for your comment. The population currently reflects the population included in the various clinical trials for benralizumab.
Comparators	AstraZeneca	The comparators are appropriate. Established clinical management without benralizumab for the relevant population includes high dose ICS-LABA ± OCS ± controller. This is reflected in the key regulatory trials for benralizumab (SIROCCO; CALIMA) as patients in both treatment arms received background treatment of medium-high dose ICS-LABA ± OCS± controller (Bleecker 2016; FitzGerald 2016). References Bleecker ER, et al. The Lancet. 2016 4;388(10056):2115-27. FitzGerald J, et al. The Lancet 2016 4;388(10056): 2128-41.	Thank you for your comment.
	BSACI	Also include omalizumab	Thank you for your comment. Omalizumab has not been included because it was not

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			considered to be a clinically relevant comparator in previous technologies in a similar population (see TA431 and TA479 for more details)
	British Thoracic Society	The comparison with Mepolizumab is important as this has a similar effect on reducing eosinophils and already has completed approval.	Thank you for your comment.
	Royal College of Physicians (RCP)	Appropriate	Thank you for your comment.
	Teva UK Limited	In addition to the comparison outline in the scope, we feel that omalizumab should also be included as a comparator, as there is an overlap population of eosinophilic and allergic asthma. Further omalizumab was a comparison in NICE STA of mepolizumab and reslizumab.	Thank you for your comment. Omalizumab has not been included because it was not considered to be a clinically relevant comparator in previous technologies in a similar population (see TA431 and TA479 for more details)
Outcomes	AstraZeneca	Yes. The outcomes are appropriate; and will capture the most important benefits and harms of the technology.	Thank you for your comment.
	BSACI	You won't be able to obtain any information on mortality from the published data	Thank you for your comment.
	British Thoracic Society	Yes. It is difficult to capture the reduction in adverse effects due to ongoing steroid use although this should be considered if possible.	Thank you for your comment. The outcomes listed are

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		Important data to look at are: 1. Data on exacerbations 2. Data on oral steroid sparing effect 3. Data on other aspects including symptoms ACQ/ACT, QOL, lung function 4. Data on nasal disease outcome (polyps are common) 5. Benefit of reduced dosing frequency vs Mepolizumab and Reslizumab.	examples and are not intended to be an exhaustive list.
	Royal College of Physicians (RCP)	Appropriate	Thank you for your comment.
	Teva UK Limited	No comment	Thank you
Economic analysis	AstraZeneca	The time horizon for the economic analysis will be a lifetime perspective.	Thank you for your comment.
	BSACI	No comment	Thank you
	British Thoracic Society	Nil	Thank you
	Royal College of Physicians (RCP)	Many patients with eosinophil driven asthma also have chronic rhinosinusitis with nasal polyps which are expensive to treat because they require repeated surgery. This should be taken into account as this technology has the potential to reduce costs in this group For asthma - prevention of exacerbations should be the major outcome measure together with an ability to withdraw oral steroids	Thank you for your comment. The evidence considered by the committee will include economic evidence around costs and quality of life. The economic analysis will incorporate the

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		and this often needs 12 months to know whether the drug is being effective	costs associated with severe asthma with elevated blood eosinophils. The outcomes for this appraisal include incidence of clinically significant exacerbations.
	Teva UK Limited	A lifetime time horizon will be required to demonstrate any differences on costs or outcomes between the technologies being compared.	Thank you for your comment.
Equality and Diversity	AstraZeneca	No equality matters are identified.	Thank you for your comment.
	BSACI	There are no obvious equality issues	Thank you for your comment.
	British Thoracic Society	Nil	Thank you
	Royal College of Physicians (RCP)	No issues	Thank you for your comment.
	Teva UK Limited	No comment	Thank you
Innovation	AstraZeneca	Yes. Benralizumab is innovative; and represents a step-change both in its potential to make a significant impact on health-related benefits; and its potential to improve how the current need is met for severe, eosinophilic asthma patients: <u>Health-related benefits</u> Benralizumab has a unique mode of action: directly targeting and causing cell death of eosinophils via natural killer cell activation,	Thank you for your comment. Potential innovation will be considered by the committee when making recommendations for benralizumab.

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		which induces rapid, and near complete depletion of eosinophils in blood and lung tissue (Bleecker 2016). As described above, the regulatory trial programme demonstrated benefits for benralizumab as an add on to background therapy versus placebo in reducing annual exacerbation rates; improving lung function; and improving asthma symptoms; and asthma-associated QoL. [redacted] which may provide significant benefits for patients as OCS use is associated with higher risks of systemic corticosteroid related complications, including infections and cardiovascular, metabolic, psychiatric, ocular, gastrointestinal, and bone-related complications (Lefebvre et al, 2015). <u>How the current unmet need is met</u> Subject to final EMA license, benralizumab will offer patients and the NHS, an anti-eosinophilic treatment with a different posology, [redacted] This may be associated with a reduction in the number of product administration visits and associated administration costs; and may give opportunities for care closer to home. <u>Health related benefits unlikely to be included in the QALY calculation</u> In providing health improvement to patients, subsequent societal benefits may be gained with the introduction of benralizumab: for example, family members who act as informal carers may be able to increase their work productivity.	

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		References Bleecker ER, et al. The Lancet. 2016 4;388(10056):2115-27. DOF BEN-021-APR2017 Lefebvre P et al J Allergy Clin Immunol 2015 136(6): 1488-1495.	
	BSACI	Definitely innovative with the potential to make a substantial impact on the health of people with asthma. Although influencing the same inflammatory pathway to mepolizumab and reslizumab it works in a different way which theoretically could be more effective. A major benefit will be reduced requirement for oral steroids which is not well reflected in QALY calculations The data is found in the Phase 2 and 3 clinical trials of benralizumab in asthma	Thank you for your comment. Potential innovation will be considered by the committee when making recommendations for benralizumab.
	British Thoracic Society	Biologic therapy for severe asthma is not unique as ant-IgE (Omalizumab) has been available for some time. Mepolizumab has also recently been evaluated favourably as an IL 5 antibody. Reslizumab is currently undergoing evaluation also as an IL 5 antibody. Benralizumab as an IL-5 receptor antibody is unique in its target receptor and therefore is innovative. Health benefits that are unlikely to be included in the QALY calculation are the benefits of not using an oral corticosteroid over long periods of time. If so there is a potential reduced risk of osteoporosis, cataracts, fractures, infection, skin thinning and diabetes. As these are future risk reductions they are unlikely to be captured in a QALY but are extremely important when considering the advantages on using a steroid sparing medication.	Thank you for your comment. Potential innovation will be considered by the committee when making recommendations for benralizumab.

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	Royal College of Physicians (RCP)	Highly innovative and with a different mechanism of action compared to mepolizumab although similar indication	Thank you for your comment. Potential innovation will be considered by the committee when making recommendations for benralizumab.
	Teva UK Limited	No comment.	Thank you
Other considerations	AstraZeneca	None	Thank you
	BSACI	Need to consider the cost and logistics of delivering the drug to the patient especially if it is to be given intravenously	Thank you for your comment. 'The technology' section now refers to subcutaneous injection.
	British Thoracic Society	The proposed medication will potentially only be given following an assessment in a severe asthma specialist centre or within a network commissioned as a centre. This should ensure quality assurance is in place that patients are only prescribed the medication if appropriate criteria are met. This would ensure that medication is given appropriately and also ensure that high cost medication is not prescribed for patients where the benefit is not likely to be seen. This also however has the potential to exclude patients in geographically remote areas who are unable or unwilling to travel to a dedicated severe asthma service.	Thank you for your comment. Potential equality issues will be discussed by the committee during the development of the appraisal. These issues will be recorded in the Equalities Impact Assessment form and will be published alongside the final scope and guidance.
	Teva UK Limited	No comment.	Thank you
Questions for consultation	Asthma UK	Asthma UK is the UK's leading asthma charity. We support people with asthma when they need us the most and fund world-leading research to find better treatments and ultimately a cure. Our goal is	Thank you for your comments. The following changes have been made to the scope:

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		to prevent asthma attacks, especially those that result in death and emergency hospitalisation. An estimated 200,000-250,000 people in the UK have severe asthma, which is a cluster of types of asthma that do not respond to current readily available treatments, rather than simply an extreme form of the condition. Benralizumab is targeted at treating those with an eosinophilic phenotype, around 40% of the total severe asthma population.[i] ***Population*** **Will benralizumab be used to treat inadequately controlled severe asthma in children and young people aged 12 years and older?** There is a substantial unmet need for people with severe asthma in the treatment options available to them. While severe eosinophilic asthma patients have recently had the first targeted therapy made available (mepolizumab), this is likely to be accessible only to a small number of the patient population. It is also only available to adult patients. Reslizumab, if approved, will similarly only be available to a restricted adult population. The CALIMA[ii] and SIROCCO[iii] phase III studies enrolled patients with severe asthma aged 12-75 years, and though the mean age of all participants within the CALIMA study was stated as 49.2 years on clinicaltrials.gov, no further detail on the specific numbers for those aged 12-17 years appears to be available. Children and young people with severe eosinophilic asthma currently have no effective targeted therapy available to them, and we hope that monoclonal antibody therapies displaying effectiveness for this population in clinical trials will be available in the future. **Is there any overlap between the population with severe persistent allergic (IgE mediated) asthma and severe asthma**	1. The population section has been amended to refer to adults only. 2. Omalizumab has not been included as a potential comparator to account for the overlap between IgE mediated asthma and severe asthma with elevated blood eosinophils. This is because omalizumab was not considered to be a clinically relevant comparator in previous technologies in a similar population (see TA431 and TA479 for more details) 3. Potential subgroups have been added to the 'other considerations' section of the scope. These subgroups are based on baseline eosinophil levels and the use of oral corticosteroids but will depend on the evidence that is available.

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		with elevated blood eosinophils inadequately controlled by inhaled corticosteroids? There will be a proportion of people with severe eosinophilic asthma that will also have elevated IgE levels, and who will also be eligible for treatment with omalizumab, though this number is difficult to estimate. There is a substantial and distinct population of patients who are not eligible for omalizumab therapy, and we would therefore advise comparison against other therapies targeted at severe eosinophilic asthma. The appraisal committee that recommended mepolizumab concluded that the comparison against omalizumab was not clinically relevant, and we believe the same approach should be adopted for consideration of benralizumab. **Will benralizumab be used to treat inadequately controlled severe persistent allergic IgE mediated eosinophilic asthma?** As highlighted above, we would expect that this overlap population may be eligible for the current monoclonal antibodies available. ***Comparators*** **Have all relevant comparators for benralizumab been included in the scope?** Yes ***Outcomes*** **Are the outcomes listed appropriate?** Yes ***Other considerations*** **Are there any subgroups of people in whom benralizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?** We believe that this will be most cost-effective for those people with severe eosinophilic asthma on regular courses of oral corticosteroids	

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		(OCS), who through reduced OCS use will be less likely to have comorbidities that require regular additional treatment. As highlighted below, this should be considered as part of the appraisal. One recent study has attempted to fill some of the evidence gap using data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma, and highlighted that comorbidities associated with long-term OCS use include type II diabetes, osteopenia/osteoporosis, dyspeptic disorders, obesity, hypertension, cataracts and obstructive sleep apnoea.[iv] **Where do you consider benralizumab will fit into the existing NICE pathway, 'Asthma'?** We would expect this to fit alongside mepolizumab in the existing pathway, available through specialised services for severe asthma. ***Innovation*** **Do you consider benralizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes. Benralizumab, while still targeting the IL-5 receptor expressed by eosinophils that mepolizumab and reslizumab target, has an innovative mode of action by binding to the receptor itself – blocking it in a more direct way.[v] **Do you consider that the use of benralizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Last month Asthma UK conducted an online survey of 1,100 people with asthma that have used OCS in the past year to find out about the side effects that they have experienced. Side effects that were identified by more than half the respondents were that they put on	

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		weight, had more difficulty falling asleep at night, felt hungrier and ate more. Emotional side effects that featured highly were that they get upset and tearful more easily, and are more irritable and feel more anxious. OCS use is a key concern for people with severe asthma due to the serious side-effects resulting from long-term use. As one of the very few treatments options available to treat severe asthma, people almost always find themselves taking very high doses of these medicines for a long time and so these serious side effects are common in this group. Estimating the impact of the effects of OCS use is a crucial area that needs to be addressed, particularly given that from a patient perspective, reduced use is a key benefit of any future treatment. References i Schleich FN, Manise M, Sele J, Henket M, Seidel L, Louis R. Distribution of sputum cellular phenotype in a large asthma cohort: predicting factors for eosinophilic vs neutrophilic inflammation. BMC Pulmonary Medicine. 2013;13:11. doi:10.1186/1471-2466-13-11. ii FitzGerald JM, Bleecker ER, Nair P, Korn S et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016 Oct 29;388(10056):2128-2141. doi: 10.1016/S0140-6736(16)31322-8. iii Bleecker ER, FitzGerald JM, Chanez P, Papi A et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet. 2016 Oct 29;388(10056):2115-2127. doi: 10.1016/S0140-6736(16)31324-1.	

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		iv Sweeney J, Patterson CC, Menzies-Gow A, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. Thorax 2016; 71: 339–346. v Menzella F, Lusuardi M, Galeone C, Facciolongo N, Zucchi L. The clinical profile of benralizumab in the management of severe eosinophilic asthma. Ther Adv Respir Dis. 2016 Dec;10(6):534-548.	
	AstraZeneca	Where do you consider benralizumab will fit into the existing NICE pathway, 'Asthma'? Benralizumab will fit into the existing NICE asthma pathway within the 'difficult or severe asthma' patient category under the 'asthma management' section. The proposed 'asthma management' NICE guideline (released for consultation in December 2016) did not include guidance for this part of the pathway related to 'difficult or severe asthma'. The proposed guideline did not provide a clear protocol for those patients who remain uncontrolled on high dose ICS + LABA therapy. In the AstraZeneca response to the guideline consultation, we called for clear step-up and referral criteria to be included in the guideline, so that patients with more severe asthma are appropriately managed as early as possible, and avoid further exacerbations.	Thank you for your comment. The NICE pathway for asthma will be updated in line with the recommendations for benralizumab.
	BSACI	A major question will be the relative positioning of omalizumab, mepolizumab, reslizumab and benralizumab. The latter three in particular all work by directly and specifically antagonising eosinophils. Whether they will all be interchangeable in their effect of have individual pros and cons is not clear at the moment. Not sure if this appraisal can answer this question however.	Thank you for your comment. This appraisal will consider mepolizumab and reslizumab as potential comparators when making recommendations for benralizumab. Omalizumab has not been included beacuse it

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			was not considered to be a clinically relevant comparator in previous technologies in a similar population (see TA431 and TA479 for more details)
	British Thoracic Society	Will benralizumab be used to treat inadequately controlled severe asthma in children and young people aged 12 years and older? *Potentially depending on safety data and trial designs.* Is there any overlap between the population with severe persistent allergic (IgE mediated) asthma and severe asthma with elevated blood eosinophils inadequately controlled by inhaled corticosteroids? *Yes. There is some overlap, however there are subgroups of patients who have normal IgE but raised eosinophils who may benefit from this medication and also ant-IgE therapy cannot be used in patients with very raised IgE out of the prescribing guidelines. This medication would be a useful alternative for them.* Will benralizumab be used to treat inadequately controlled severe persistent allergic IgE mediated eosinophilic asthma? *As above.* Have all relevant comparators for benralizumab been included in the scope? *Yes* Are the outcomes listed appropriate? *Yes*	Thank you for your comments. The following changes have been made to the scope: 1. The population section has been amended to refer to adults only. 2. Omalizumab has not been included as a potential comparator to account for the overlap between IgE mediated asthma and severe asthma with elevated blood eosinophils. This is because omalizumab was not considered to be a clinically relevant comparator in previous technologies in a similar population (see TA431 and TA479 for more details) . 3. Potential subgroups have been added to the 'other considerations' section of the

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		Are there any subgroups of people in whom benralizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? *Those with higher eosinophils and increased numbers of exacerbations per year would likely benefit more. As you have stated for Mepolizumab: blood eosinophil count >300 and 4 or more exacerbations in 12 months.* Where do you consider benralizumab will fit into the existing NICE pathway, 'Asthma'? *Benralizumab would be included in the difficult or severe asthma section.* 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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which benralizumab will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. 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 tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.	scope. These subgroups are based on baseline eosinophil levels and the use of oral corticosteroids but will depend on the evidence that is available. Potential equality issues will be discussed by the committee during the development of the appraisal. These issues will be recorded in the Equalities Impact Assessment form and will be published alongside the final guidance.

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		As noted above. This medication is for those patients that fall into the severe category and therefore NHSE specialist commissioned centres would therefore need to approve its use. Potentially patients who are geographically remote from these centres who are unable or unwilling to travel for assessment may be excluded from access. Those unable to travel could include vulnerable patients or those unable to afford to travel. Do you consider benralizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? *As noted above. Benralizumab is not unique in its action on affecting the IL-5 cytokine, however its target receptor is unique in that it targets IL-5Ra. The increasing availability of additional medication to treat severe difficult to control asthma over and above oral corticosteroids is a definite step change in the management of the condition with a potential to greatly improve quality of life and reduce morbidity.* Do you consider that the use of benralizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? *Answered above. Health benefits that are unlikely to be included in the QALY calculation are the benefits of not using an oral corticosteroid over long periods of time. If so there is a potential reduced risk of osteoporosis, cataracts, fractures, infection, skin thinning and diabetes. As these are future risk reductions they are unlikely to be captured in a QALY but are extremely important when considering the advantages on using a steroid sparing medication.*	

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		Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. *Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. The Lancet, Volume 388, Issue 10056, 29 October–4 November 2016, Pages 2115–2127* NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).	
	Royal College of Physicians (RCP)	This appraisal should follow similar lines to TA431	Thank you for your comment. We have listed TA431 as a related technology appraisal.
	Teva UK Limited	No comment.	Thank you
Additional comments on the draft scope	BSACI	No	Thank you for your comment.
	British Thoracic Society	This is an important area of medication to evaluate for a group of patients who are significantly affected by their condition who have few options to control their disease. They consume significant amounts of health resources and although expensive there is an opportunity to improve morbidity, mortality and offset the potential future economic burden of the adverse effects of long term oral corticosteroid use.	Thank you for your comment.

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	Royal College of Physicians (RCP)	Asthma is heterogenous in its presentation and that complexity is best expressed as the relationship between airway dysfunction as measured by variability in lung function and airway inflammation as measured by induced sputum, exhaled nitric oxide, a blood eosinophil count or other measures of TH2 like inflammatory responses. Most asthma is eosinophilic in the sense of there being an increased number of eosinophils in the airway and blood. This reflects a Th2 pattern of inflammation which leads to the production of increased amounts of a cytokine called IL-5 which is a specific growth factor for eosinophils. IL-5 is released by Th2 lymphocytes and a newly described class of innate cells called innate lymphoid cells type 2. In most patients with asthma the Th2 response results in increased amounts of specific IgE. However in a significant proportion of asthmatics particularly those of adult onset the asthma and eosinophilia occur without increased IgE. The triggers driving this inflammatory process in this group of patients is not clear although the likelihood is that it is a non-IgE mediated ILC2 mediated allergic process to an unknown allergen. In both IgE and non-IgE mediated asthma the process is driven by IL-5 and inhibited by benralizumab. The degree of eosinophilia associated with asthma varies considerably with a proportion of patients including those of adult onset having a marked blood and tissue eosinophilia. It is likely these patients will do particularly well with benralizumab. An important concept in asthma is that the abnormal physiology although linked to inflammation can be independent of it. In addition the symptoms associated with disordered lung function (chest tightness, wheeze, bronchodilator responsive episodic shortness of breath) are distinct from those associated with inflammation (cough, progressive bronchodilator resistant breathlessness leading to severe exacerbations). Traditionally most asthma drugs have been measured against their effect on lung function and this hampered the	Thank you for your comment. The committee will consider the clinical and cost effectiveness evidence as part of the development of this technology appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
		development of mepolizumab because it has relatively little effect on the variable airflow obstruction component of asthma with its main effect being a reduction in exacerbations. Benralizumab will therefore be of greatest benefit in patients whose main problem is severe exacerbations irrespective of the degree to which they have bronchodilator reversibility, airway hyperresponsiveness. It is therefore important that the inclusion criteria and measures of benefit are taken into account.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope