National Institute for Health and Care Excellence

Health Technology Evaluation

Benralizumab for treating relapsing or refractory eosinophilic granulomatosis with polyangiitis [ID6266]
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	AstraZeneca	AstraZeneca consider the proposed evaluation route to be appropriate.	Comment noted. No action required.
	British Society of Rheumatology	Yes, this topic is appropriate for an evaluation. For example, the findings of a ten-year study carried out by Norfolk and Norwich University Hospitals NHS Foundation Trust on the incidence of small vessel vasculitis which included EGPA, were presented at the EULAR Conference in June 2024. The annual incidence of EGPA was found to be 2.6/million (REF doi 10.1136/annrheumdis-2024-eular.1284); clinicians involved in the study have reported that every single patient in the study had relapsed at least once and therefore they would all have benefited from benralizumab and would have been eligible for benralizumab. This experience differs from published data because the relapse rates from studies have been subject to changes in the definition of relapse (REF 10.1136/ard.2007.071936)	Comment noted. No action required.

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	British Thoracic Society	We agree that this is clinically relevant and an important single technology appraisal in a population with significant unmet need.	Comment noted. No action required.
	UK Kidney Association	An important disease indication for evaluation; STA seems appropriate.	Comment noted. No action required.
	Vasculitis UK	Single technology appraisal	Comment noted. No action required.
	NHS England Specialised Commissioning	This is a much needed evaluation since there is a significant burden arising from disease that is resistant to or relapses after currently available treatment. STA is appropriate. This agent is included in expert guidelines and treatment pathways in various countries in Europe and North America. The evaluation would reflect the advanced understanding of the pathophysiology of the disease and new trial data.	Comment noted. No action required.
Wording	AstraZeneca	The appropriate patient population for this appraisal are adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA), receiving oral corticosteroids (OCS) with or without stable immunosuppressive (IS) therapy. The wording of the remit should reflect the population to be appraised, in line with the pivotal trial MANDARA, [redacted]. AstraZeneca, therefore, kindly request the wording to be updated to “to appraise the clinical and cost-effectiveness of benralizumab as an add-on treatment for adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA)”.	Comment noted. The title and remit have been updated. The term ‘add-on treatment’ has been added to the section which describes the technology.

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	British Society of Rheumatology	It is important that the wording reflects the fact that the control of vasculitis will lead to longer term benefits by, for example, a reduction of the cardiovascular complications that we know are a sequela of uncontrolled inflammation i.e. the issue of comorbidities should clearly be reflected in the wording when considering cost-effectiveness.	Comment noted. The wording has been updated to reflect that without treatment, life-threatening complications may develop. The specific benefits of treatment will be considered by committee during the evaluation.
	British Thoracic Society	We are unclear why the scope is worded Benralizumab 'with corticosteroids' . If the word corticosteroids is included, then it should be clarified if this is inhaled or oral.	The scope has been updated to reflect that benralizumab will be used as an add-on to existing therapies.
	UK Kidney Association	Yes, wording appropriate.	Comment noted. No action required.
	Vasculitis UK	Yes, wording appropriate.	Comment noted. No action required.
	NHS England Specialised Commissioning	Yes, wording appropriate.	Comment noted. No action required.

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Timing Issues	AstraZeneca	EGPA is a rare form of vasculitis with a high clinical unmet need. EGPA is a highly heterogenous disease, and patients experience a wide variety of clinical manifestations that can impact multiple organs simultaneously. EGPA has a significant impact on health-related quality of life (HRQoL) owing to substantial fatigue, functional impairment, and limitations to daily activities due to symptom burden.[1,2] Given the rarity of EGPA, its heterogenous clinical presentation and the clinical overlap with other vasculitic or eosinophilic disorders, the diagnosis of EGPA is often challenging. Interviews with patients revealed that it takes several years for them to be diagnosed. Owing to a lack of established treatment pathway, patients navigate between various departments and consultants and undergo several tests and scans before being referred to the correct specialists. During this lengthy process, patients' conditions are not improving, there is a detrimental impact on their mental health, and it leaves patients feeling unsupported. In the UK, there are no approved therapies for EGPA specifically. Therefore, when patients are finally diagnosed, they have limited treatment options. The treatment goal in EGPA is to induce and maintain remission. Clinicians are currently using chronic, high-dose oral corticosteroids* (OCS) and IS to achieve this treatment goal. OCS-related toxicity such as long-term complications, e.g. cardiovascular disease, diabetes, and osteoporosis [3-5] is particularly relevant to patients with EGPA as they are often exposed to high cumulative doses. Patients treated with IS are at high risk of organ toxicity such as cytopenia, hepatotoxicity and major infections. [3,4, 6-8] In addition, ~83% of patients experience a relapse, [9,10] which is associated with a higher mortality risk and increased healthcare resource use. [9,11] Interviews with patients, a multi-disciplinary cohort of clinicians involved in the management of this disease (pulmonologists, rheumatologists, vasculitis	Comment noted. No action required.

Section	Stakeholder	Comments [sic]	Action
		consultants) and patient advocacy groups (PAGs) all highlighted the acute unmet need in EGPA. It is of utmost urgency to provide an additional treatment option to this niche group of patients who have been neglected. Therapies are needed that help patients achieve durable remission, avoid relapses, while also enabling OCS dose reduction to avoid the detrimental side-effects and long-term complications associated with current treatment options. Benralizumab has the potential to address the high unmet need and all these challenges.	
	British Thoracic Society	There is urgency in this evaluation due to the absence of any other evidence-based treatment for EGPA and the significant side effects associated with steroids.	Comment noted. No action required.
	UK Kidney Association	There is relative urgency for patients – since there are no licensed alternatives to steroids for EGPA in the UK, and no unlicensed alternative with compelling evidence base for efficacy.	Comment noted. No action required.
	Vasculitis UK	In the rare disease community any medication that can improve patients outcomes or quality of life should be evaluated the soonest possible.	Comment noted. No action required.
	NHS England Specialised Commissioning	This is urgently required given that only those with the severe asthma phenotype of this disease can currently access this evidence based medicine and then only in a designated severe asthma centre. As such many patients with “severe disease” for EGPA overall cannot access the drug unless they have the severe asthma phenotype and are in the correct hospital, as this is what is in line with TA 565. This needs to be urgently addressed as current situation is inequitable and misses the most severe cases as defined by the Five Factor Score (FFS). A timescale of months is suggested for this evaluation.	Comment noted. No action required.

Section	Stakeholder	Comments [sic]	Action
Additional comments on the draft remit			

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	**Proportion of patients experiencing a relapse** AstraZeneca notes that the background information states "around 50% of people experience a relapse after treatment within 5 years" – this is sourced from a non-EGPA specific population (ANCA-associated vasculitis). Estimates from literature indicate that the relapse rate is likely to be higher in an EGPA-specific population. A preliminary estimate is approximately 83%, but more evidence will be presented in the Company submission. [9,10] **Maintenance treatments** The background information cites the following as maintenance treatments: • Cyclophosphamide • Methotrexate • Azathioprine Based on clinical guidelines and initial clinician feedback, AstraZeneca believes the maintenance treatments used in UK clinical practice are as follows, and the rationale is further detailed below. • Oral corticosteroids (OCS)	Comment noted. The background section has been updated to note that 'Over 50%' of people experience relapse. NICE was unable to verify the 83% figure but invites the company to include this information in its submission. The background section has been updated to reflect that cyclophosphamide is used to induce remission and not as a maintenance treatment. The scope states that

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		• Immunosuppressive agents (e.g. methotrexate, azathioprine, mycophenolate mofetil) For severe disease (defined as vasculitis with life- or organ-threatening manifestations), both the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) guidelines recommend initiating cyclophosphamide (or rituximab if cyclophosphamide is unsuitable) to induce remission. [6,8] Cyclophosphamide has significant side effects including gonadal toxicity inducing premature ovarian failure, bone marrow depression and infection, haemorrhagic cystitis, and an increased risk of future uroepithelial (bladder) cancer. [12] Therefore, it is not well suited for long-term use as a maintenance treatment. Preliminary interviews with clinicians indicate that they are keen to avoid cyclophosphamide-induced organ-threatening toxicity and, therefore, only use it in ~20% of patients to induce remission, and not as a maintenance treatment. Rituximab can be used to induce remission where cyclophosphamide is unsuitable. As per the NHS England clinical commissioning policy, and substantiated by initial feedback from clinicians, rituximab is not commonly used as a maintenance treatment, and its use is likely to be greatly limited in UK clinical practice, given the restriction criteria for commissioning.[13] In summary, based on clinical guidelines and initial clinician feedback, AstraZeneca strongly believes that cyclophosphamide is only used in a low proportion of patients (~20%) to induce remission – not as a maintenance treatment. Rituximab can be used to induce remission when cyclophosphamide is unsuitable – and is unlikely to be commonly used as a maintenance treatment in UK clinical practice.	rituximab may be used to induce remission when cyclophosphamide is unsuitable (and does not suggest it is commonly used as maintenance treatment).

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		Instead, maintenance treatments most used in UK clinical practice include OCS and immunosuppressive agents (e.g. methotrexate, azathioprine, mycophenolate mofetil). AstraZeneca, therefore, kindly request the wording of the background information to be updated accordingly.	
	British Thoracic Society	1. The background should emphasise the absence of any other effective treatment for maintenance of remission 2. The background should clarify that the treatments listed (methotrexate, azathioprine, rituximab)do not have a robust evidence base in EGPA; the data is largely extrapolated from studies on ANCA-positive vasculitis that did not include patients with EGPA	Comment noted. The high rate of relapse is noted within the background section. The clinical benefits of benralizumab versus its comparators will be considered during the technology appraisal process.
	UK Kidney Association	This is brief, but summaries key aspects of the disease and current treatment.	Comment noted. No action required.
	Vasculitis UK	I would add that EGPA is the rarest of ANCA associated vasculitides, it can be fatal and is definitely life changing.	Comment noted. The background section notes that EGPA is rare and that life-threatening or fatal complications may develop.

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	NHS England Specialised Commissioning	This would benefit from additional description of severe disease (non-asthma) and the validated FFS (Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Toumelin P Le, et al. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine. 2011 Jan;90(1):19–27).	Thank you for your comment and the information. The scope is intended to be a brief summary of the topic area. We have added some information regarding the Five Factor Score and will note the additional information for the technology appraisal.
Population	AstraZeneca	The appropriate patient population for this appraisal are adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA), receiving oral corticosteroids (OCS) with or without stable immunosuppressive (IS) therapy. The wording of the remit should reflect the population to be appraised, in line with the pivotal trial MANDARA, [redacted]. AstraZeneca, therefore, kindly request the wording to be updated accordingly.	Comment noted. The population has been updated.
	British Thoracic Society	Yes	Comment noted. No action required.
	UK Kidney Association	Will children <18 years be included?	The population for this appraisal is adult patients, in line with the population for the

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			MANDARA trial (NCT04157348).
	Vasculitis UK	Yes	Comment noted. No action required.
	NHS England Specialised Commissioning	Yes	Comment noted. No action required.
Subgroups	AstraZeneca	AstraZeneca does not believe subgroup analyses are appropriate for the following reasons: • The patient population in MANDARA reflects the expected heterogeneity of the disease and is representative of the patient population that is likely to be treated in UK clinical practice • Given the rarity of EGPA, and the sample size of 70 patients in the benralizumab arm of MANDARA, it will be challenging to conduct subgroup analyses as statistical estimates from further splicing small patient numbers might be unreliable • If the recommendation was optimised for specific subgroups, implementation in clinical practice would present significant challenges Furthermore, AstraZeneca considers severe EGPA to represent patients having vasculitis with life- or organ-threatening manifestations. Such patients were excluded from the pivotal trial MANDARA, and therefore, this subgroup is not appropriate to be considered.	Following input from stakeholders, the subgroups have been removed from the scope.
	British Thoracic Society	It is unclear to us why the listed subgroups have been chosen as there is no real evidence to support a differential response to benralizumab in these groups.	Following input from stakeholders, the subgroups have been

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			removed from the scope.
	UK Kidney Association	Precise definition of 'severe' disease will be required – see below	Comment noted. This is no longer applicable as the subgroup has been removed from the scope.
	Vasculitis UK	Yes	Comment noted. Following input from stakeholders, the subgroups have been removed from the scope.
	NHS England Specialised Commissioning	The subgroups are appropriate but should not be restricted to these; perhaps consider ANCA negative patients; those without asthma; renal and neurological involvement	Comment noted. Following input from stakeholders regarding the lack of evidence to support a differential response to benralizumab in these subgroups, the subgroups have been removed from the scope.
Comparators	AstraZeneca	AstraZeneca believes the most appropriate comparator is a weighted average of the most used agents as part of UK clinical practice.	The comparators are kept inclusive at this stage. The company is

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		From preliminary interviews with relevant clinicians, AstraZeneca believes the most used agents as maintenance treatments are: • Oral corticosteroids (OCS) • Immunosuppressive agents (e.g. methotrexate, azathioprine, mycophenolate mofetil) AstraZeneca is currently conducting a Clinical Practice Research Datalink (CPRD) analysis, which will help inform these proportions. Furthermore, AstraZeneca will also seek to validate these proportions of patients receiving each treatment, from further interviews with clinicians, prior to the submission. These proportions will inform the weighted average comparator arm of the economic model. AstraZeneca believes that cyclophosphamide and rituximab are not appropriate comparators. As mentioned in the "background information" section above, cyclophosphamide is only used in a limited number of patients (~20%) and only to induce remission – not as a maintenance treatment, due to concerns of cyclophosphamide-induced organ-threatening toxicity. Rituximab can be used to induce remission where cyclophosphamide is unsuitable. As per the NHS England Clinical commissioning policy, and substantiated by initial feedback from clinicians, rituximab is not commonly used as a maintenance treatment, and its use is likely to be greatly limited in UK clinical practice, given the restriction criteria for commissioning.[13] AstraZeneca, therefore, kindly request the comparators and the relevant sections in the draft scope are updated accordingly.	invited to justify if/why any comparators are not relevant or feasible in its submission.
	British Thoracic Society	Yes and as detailed, none of the listed treatments currently have a marketing authorisation in the UK for this indication.	Comment noted. No action required.

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	UK Kidney Association	Yes, these are all standard alternative treatments.	Comment noted. No action required.
	Vasculitis UK	Yes	Comment noted. No action required.
	NHS England Specialised Commissioning	Yes, though the caveat would be that none are licensed and for rituximab, which is currently most often used for refractory or severe cases, the evidence and rationale is not completely clear cut, especially in those patients who have a diagnosis of EGPA but who are negative for ANCA antibodies (which is a significant proportion). Opinion is divided amongst experts as to the broad efficacy of rituximab across EGPA, other than its potential benefit in ANCA positive cases, unlike its use overall for ANCA associated vasculitis or SLE.	Comment noted. No action required.
Outcomes	AstraZeneca	AstraZeneca believes most listed outcomes are appropriate with the following exceptions: • "Number and severity of relapses" o Relapses are captured by health state transitions but no stratification by severity is available from MANDARA o Furthermore, stratification of relapses is not common in UK clinical practice, and would be difficult to measure consistently • "Cumulative dose of immunosuppressants" o MANDARA was not designed to assess IS dosing, and this was not powered as an endpoint o Furthermore, capturing cumulative dose would be challenging, given the variability in IS dosing in MANDARA	Comments noted. • Severity of relapses has been removed • Cumulative dose of immunosuppressants has been replaced with 'use of

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		▪ This variability is also observed in UK clinical practice due to heterogenous practices • "Pulmonary function" o Pulmonary function was captured at baseline and several points over the study period of MANDARA o These data will be presented in the Company submission o However, these are not included in the economic model; the dysfunction of EGPA is captured in an aggregate approach via the Birmingham Vasculitis Activity Score (BVAS) tool – rather than focusing on one particular organ system ▪ BVAS is a validated tool to assess of disease activity in patients with many different forms of vasculitis AstraZeneca, therefore, kindly request the draft scope to be updated accordingly.	immunosuppressants. • Pulmonary function remains unchanged. The company is invited to justify if/why any outcomes are not included in its submission or cost-effectiveness model.
	British Thoracic Society	We would recommend- 1. Reduction in steroid use should be clarified as 'reduction in systemic steroid use' 2. Additional outcome measure: Cessation of systemic corticosteroids We do not feel that the following outcomes are appropriate for this indication: 1. Total accrued duration of remission 2. Cumulative dose of immunosuppressants 3. Pulmonary function	Comments noted. The outcomes have been updated to include cessation of steroid use, and to specify this is systemic steroid use. Outcomes are kept inclusive at this stage, and the company is invited to justify if/why any outcomes are not included in its submission. Accrued

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			duration of remission and pulmonary function were included as outcomes in the MANDARA trial (NCT04157348).
	UK Kidney Association	Measures of healthcare resource utilisation?	As noted in section 2.2.22 of the NICE manual for health technology evaluations, the potential effect on resource costs and savings that would be expected from introducing the technology should be included in the cost-effectiveness analysis which is submitted by the company.
	Vasculitis UK	Yes	Comment noted. No action required.
	NHS England Specialised Commissioning	Yes	Comment noted. No action required.
Equality	AstraZeneca	N/A	Comment noted. No action required.

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	British Thoracic Society	No change needed	Comment noted. No action required.
	UK Kidney Association	No concerns	Comment noted. No action required.
	NHS England Specialised Commissioning	Analysis should take into account that cyclophosphamide can cause infertility (And likely will do so at doses needed for EGPA) so women of childbearing age potentially face a disproportionate harm from this therapy.	Comment noted. This potential equalities issue can be considered by the committee during the appraisal process.
Other considerations	AstraZeneca	N/A	Comment noted. No action required.
	British Society of Rheumatology	We have no particular comment, other than that a wide range of patient groups should be given the opportunity to comment on the scoping documents, which we note from the stakeholder list is the case.	Comment noted. No action required.
	Vasculitis UK	N/A	Comment noted. No action required.
Questions for consultation	AstraZeneca	**Q1. What is established clinical management for relapsing or refractory eosinophilic granulomatosis with polyangiitis?**	Comment noted. No action required.

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		For the treatments used in the management of EGPA, please refer to AstraZeneca's consultation response under "comparators" section of the draft scope. For the prescribing and follow-up in the management of EGPA, please refer to AstraZeneca's consultation response to Q7 of the "Questions for consultation" section below. **Q2. Does established clinical management in the NHS differ for people with severe vs non-severe disease? If so, how? How is severe disease defined?** AstraZeneca considers severe EGPA to be vasculitis with life- or organ-threatening manifestations, and non-severe EGPA as vasculitis without life- or organ-threatening manifestations. Disease management of severe EGPA differs from non-severe EGPA. Although there are some differences in the treatment algorithms outlined in the ACR and EULAR guidelines, both recommend initiating cyclophosphamide (or rituximab if cyclophosphamide is unsuitable) to induce remission for severe disease. [8,10] Once patients have achieved remission, disease management would switch to maintenance treatments such as azathioprine or methotrexate. These treatments would be administered alongside OCS – the aim would be to taper them to the minimum effective dosage to reduce long-term toxicity. Patients with life- or organ-threatening EGPA were excluded from the pivotal trial MANDARA. For vasculitis without life- or organ-threatening manifestations, EGPA is managed with OCS with or without IS therapy. The aim would be to taper OCS to the minimum effective dose to reduce long-term toxicity and consider a reduction in the dose of IS to limit the risk of complications.	Comment noted. No action required.

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		Q3. Where do you consider benralizumab will fit into the existing care pathway for relapsing or refractory eosinophilic granulomatosis with polyangiitis? Benralizumab will be an add-on treatment to OCS with or without IS therapy, for adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis. **Q4. What proportion of people with relapsing/refractory EGPA are already eligible for benralizumab to treat severe eosinophilic asthma (given the population specified in NICE technology appraisal 565)?** Given the challenge in diagnosing EGPA and limited literature available owing to the rarity of the disease, it is difficult to establish the exact proportion of patients who have EGPA and are co-morbid with severe asthma (SA). A CPRD analysis estimates 24% of patients with EGPA have comorbid SA;[11] however, based on initial feedback from clinicians, they suspect it is closer to 50%. AstraZeneca conducted a literature review and three studies (pooled N=333) reported on average 57.9% of patients had severe asthma according to Global Initiative for Asthma (GINA) Step 5. [14-16] AstraZeneca will be conducting further interviews with relevant clinicians to ascertain clarity on this proportion. AstraZeneca seeks to highlight that the dose of benralizumab differs between SA [30 mg every 4 weeks (Q4W) for the first 3 doses, then every 8 weeks (Q8W) thereafter] and EGPA (30mg Q4W). Accessing benralizumab at the SA dose is challenging even for a co-morbid patient with EGPA and SA, given the various hurdles around eligibility criteria for benralizumab, access to SA centres and low bio-penetration (biologic uptake) rate. Please refer to AstraZeneca's consultation response under Q6 for further context.	Comment noted. No action required. Comment noted. No action required.

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		Q5. How many people with relapsing/refractory EGPA would be expected to benefit from benralizumab that are not currently eligible for treatment? AstraZeneca interprets this question as the total number of patients who are currently diagnosed with EGPA in the UK, receiving OCS with or without IS therapy, and are relapsing/refractory and hence would be eligible for treatment with benralizumab, as an add-on therapy. AstraZeneca have estimated ~2,000 patients in the UK with EGPA who are diagnosed, receiving OCS with or without IS therapy. [17-21] Approximately 83% of these patients [9,10] (~1,700 patients) are relapsing/refractory and would, therefore, be eligible for treatment with benralizumab. **Q6. Where people with relapsing/refractory EGPA are already taking benralizumab for asthma, do they typically take the licensed dose for severe eosinophilic asthma (30 mg every 4 weeks for the first 3 doses, then every 8 weeks thereafter)?** From preliminary interviews with respiratory consultants, benralizumab is used in patients with EGPA at the licensed dose in severe eosinophilic asthma (SA), i.e. 30 mg every 4 weeks (Q4W) for the first 3 doses, then every 8 weeks (Q8W) thereafter. Clinicians expressed frustration at the inability to control patients' symptoms at the SA dose and have a strong desire to have access to the dose investigated and proved to be efficacious in MANDARA for EGPA [30mg Q4W). The less frequent asthma dose (30mg Q8W) has not formally been tested in EGPA, and most real-world data is from patients with asthma and EGPA manifestations. A more frequent dose (30mg Q4W) is considered necessary	Comment noted. No action required. Comment noted. No action required.

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		for EGPA because it is a more severe disease than asthma, and the eosinophil (EOS) load is often higher.[21] Patients with EGPA and co-morbid SA would only be able to access benralizumab, if they meet the eligibility criteria for its recommendation within SA, i.e. based on blood eosinophil count, prior exacerbation history and being inadequately controlled despite maintenance therapy with high-dose inhaled corticosteroids and long-acting beta-agonists. Even if patients are eligible for benralizumab in SA, after meeting these criteria, it is widely understood that access to SA centres in England (where benralizumab is prescribed for SA) is challenging. Despite the inclusion of SA biologics in the NHS England Rapid Uptake Products (RUP) programme 2021/2022, the bio-penetration (biologic uptake) rate is still [redacted] in this group of patients, based on AstraZeneca's estimates.[22] Furthermore, not all patients with EGPA have SA (the exact proportion of these patients remains to be determined). Therefore, AstraZeneca firmly believes that benralizumab needs to be made available for all eligible EGPA patients, at the dose that was investigated and proved to be efficacious. **Q7. Please select from the following, will benralizumab with corticosteroids be:** A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): AstraZeneca anticipates the prescribing/initiation of benralizumab to be via specialist care (tertiary care). The management of EGPA is multi-disciplinary,	Comment noted. No action required.

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		i.e. it includes clinicians from various disciplines such as severe asthma specialists, rheumatologists, nephrologists, neurologists, cardiologists and ear, nose, throat (ENT) specialists. Once patients have achieved remission and can be discharged from a specialist's care, patients could self-administer benralizumab at home (Homecare). AstraZeneca estimates there are 35 centres for EGPA in England; these are defined as vasculitis clinics which are part of academic centres or centres where a specialist (from the list above) will be available to treat an EGPA patient. **Q8. For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** Preliminary insights dictate that the setting for prescribing and routine follow-up for comparators and subsequent treatments would follow the same pattern as the intervention, i.e. initiated in tertiary care, with routine follow-up until patients can be discharged from the specialist's care. **Q9. Would benralizumab be a candidate for managed access?** AstraZeneca does not consider benralizumab in this setting to be a candidate for managed access as there are no uncertainties as such which would be resolved by collecting further data. **Q10. Do you consider that the use of benralizumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Given the lack of approved therapies, patients with EGPA have limited treatment options. These existing treatment options are associated with significant burdensome toxicity and complications, which result in a detriment to their HRQoL.	Comment noted. No action required. Comment noted. No action required. Comment noted. The company is invited to include this information

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		Benralizumab offers better remission rates and longer periods of remission compared with standard of care. Therefore, after achieving remission patients could be discharged from specialist care and self-administer benralizumab at home (Homecare). This convenience of administration can ease some of the burden of living with EGPA, such as saving the time and cost of travel, potentially having to arrange childcare and/or impact employment. Additionally, once patients are on Homecare, they will be monitored by one specialist (rather than having multiple specialists involved in their care prior to discharge). This puts less pressure on NHS resources as well as making patients feel more supported by having continuity in their care. These benefits are not explicitly captured in the economic model. **Q11. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** N/A	within its evidence submission to NICE. Comment noted. No action required.
	British Thoracic Society	***What is established clinical management for relapsing or refractory eosinophilic granulomatosis with polyangiitis?*** This has been covered ***Does established clinical management in the NHS differ for people with severe vs non-severe disease? If so, how? How is severe disease defined?***	Comment noted. No action required.

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		We do not feel that the evaluation should be based on severe vs non-severe. EGPA can be characterised as 'relapsing' or 'in remission'	Comment noted. No action required.
		Where do you consider benralizumab with corticosteroids will fit into the existing care pathway for relapsing or refractory eosinophilic granulomatosis with polyangiitis? 1. To induce remission in patients with no evidence of life/organ-threatening disease 2. Enable tapering of systemic steroids in patients who have been unable to achieve clinical remission following induction therapy with other immunosuppressants 3. Failure to achieve clinical remission following initial induction therapy	Comment noted. No action required.
		What proportion of people with relapsing/refractory EGPA are already eligible for benralizumab to treat severe eosinophilic asthma (given the population specified in NICE technology appraisal 565)? We are not aware that this analysis has been done.	Comment noted. No action required.
		How many people with relapsing/refractory EGPA would be expected to benefit from benralizumab that are not currently eligible for treatment? **Currently, no patients are eligible for the 4-weekly dose of benralizumab for EGPA. Published data suggests about two thirds of EGPA patients treated with benralizumab achieve clinical remission on treatment.** ***Where people with relapsing/refractory EGPA are already taking benralizumab for asthma, do they typically take the licensed dose for***	

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		severe eosinophilic asthma (30 mg every 4 weeks for the first 3 doses, then every 8 weeks thereafter)? Yes, they take the dose licenced for severe eosinophilic asthma ***Please select from the following, will benralizumab with corticosteroids be***: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): D- As this is a rare disease, we would anticipate and recommend benralizumab for EGPA is only prescribed in commissioned severe asthma and vasculitis centres. These are mostly in tertiary care. ***For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.*** No, all follow-up should be in the specialist centre that has prescribed the biologic. ***Would benralizumab with corticosteroids be a candidate for managed access?*** Yes. Current real world evidence exists with the 'asthma dose' but not the 4-weekly dose that was used in the clinical trials.	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Do you consider that the use of benralizumab with corticosteroids can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? A reduction in the short- and long-term steroid related morbidity ***Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.*** We could support with the literature review when it is done. It is likely that much of this data will need to be extrapolated from the severe asthma data but also other inflammatory diseases where steroids are used. Not specifically for EGPA, but: There is a large amount of data available that highlights the harms associated with systemic steroids in a dose-dependent way. We can provide these references if needed. There is also published data that shows reduction in risk of steroid side effects 12-months after cessation of systemic steroids.	Comment noted. No action required. Comment noted. The company and stakeholders are invited to include information on these potential benefits in their submissions during the appraisal process.
	UK Kidney Association	**What is established clinical management for relapsing or refractory eosinophilic granulomatosis with polyangiitis?**	

Section	Consultee/ Commentator	Comments [sic]	Action
		In the UK, EGPA is exclusively managed in secondary care, and largely in specialist respiratory or vasculitis services. First-line treatment is with glucocorticoids. In patients with relapsing or steroid-dependent disease, conventional DMARDS (e.g. MMF, azathioprine) are often used to lower glucocorticoid burden and to reduce relapse risk, though there are limited controlled data for their efficacy. In patients with severe disease manifestations, remission-induction treatment with cyclophosphamide or rituximab (using protocols established in RCT for other forms of systemic vasculitis) are often used, though patients with EGPA were not specifically included in many of these studies. More recently, patients with severe asthma as a manifestation of EGPA may receive anti-IL5 therapy (e.g mepolizumab, benralizumab) or other biologics (e.g. Tezepelumab) via existing commissioned routes in specialist asthma services. Evidenced-based consensus recommendations for treatment of EGPA include: American College of Rheumatology: https://pubmed.ncbi.nlm.nih.gov/34235894/ European Alliance of Associations for Rheumatology: https://pubmed.ncbi.nlm.nih.gov/36927642/ European EGPA Study Group: https://pubmed.ncbi.nlm.nih.gov/37161084/	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Does established clinical management in the NHS differ for people with severe vs non-severe disease? If so, how? How is severe disease defined? Yes, as above. In the above treatment recommendations, severe disease is generally defined by the Five-Factor Score (renal insufficiency, proteinuria, cardiomyopathy, gastrointestinal tract and central nervous system involvement) as well as peripheral neuropathy and other rare manifestations (for example, alveolar haemorrhage, digital ischaemia). Non-severe disease is defined by absence of life- or organ-threatening manifestations (e.g., rhinosinusitis, mild systemic symptoms, mild inflammatory arthritis, skin involvement without ulceration, skeletal muscle myositis) **Where do you consider benralizumab with corticosteroids will fit into the existing care pathway for relapsing or refractory eosinophilic granulomatosis with polyangiitis?** As first line treatment for patients with non-severe relapsing disease; as a potential adjunct treatment in patients with severe relapsing disease; as adjunct treatment for patients with steroid-dependent (severe or non-severe) disease.	Comment noted. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		What proportion of people with relapsing/refractory EGPA are already eligible for benralizumab to treat severe eosinophilic asthma (given the population specified in NICE technology appraisal 565)? Estimate 50-60% • **How many people with relapsing/refractory EGPA would be expected to benefit from benralizumab that are not currently eligible for treatment?** The remainder **Where people with relapsing/refractory EGPA are already taking benralizumab for asthma, do they typically take the licensed dose for severe eosinophilic asthma (30 mg every 4 weeks for the first 3 doses, then every 8 weeks thereafter)?** Yes **Please select from the following, will benralizumab with corticosteroids be:** **A.** ~~**Prescribed in primary care with routine follow-up in primary care**~~ **B.** ~~**Prescribed in secondary care with routine follow-up in primary care**~~ **C. Prescribed in secondary care with routine follow-up in secondary care**	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		D. ~~Other (please give details):~~ **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention**. As above **Would benralizumab with corticosteroids be a candidate for managed access?** Yes – could be used, for example, to acquire data on efficacy of the above 'asthma' dosing regimen in patients with EGPA; for disease manifestations that we excluded or poorly represented in the clinical trial programme for benralizumab; on efficacy beyond 1 year. **Do you consider that the use of benralizumab with corticosteroids can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** No **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** N/A	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Vasculitis UK	N/A	Comments noted. No action required.
	NHS England Specialised Commissioning	Place in treatment would be helpful for use, possibly as first line, in severe i.e. organ or life-threatening disease whether at first presentation or relapse; otherwise, disease that is not responding to available therapy and disease that has relapsed despite currently available therapy. Patients should not have had to have rituximab first or cyclophosphamide (given the infective and infertility toxicity associated with that). Patients do take the asthma dose but this is not the dose used in trials of benralizumab in EGPA. Option C for treatment management for this agent and comparators Yes for managed access by Specialist Rheumatology and Respiratory services	Comments noted. No action required.
Additional comments on the draft scope	British Thoracic Society	We this this scope should be on benralizumab for the management of EGPA. It does not need to include 'steroids'	Comment noted. The title has been updated.

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

Immunodeficiency UK