NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Berotralstat for preventing recurrent attacks of hereditary angioedema [ID1624]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Berotralstat for preventing recurrent attacks of hereditary angioedema [ID1624]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Comments on the Appraisal Consultation Document from BioCryst Pharmaceuticals**
   a. ACD comments form
   b. ACD comments appendix

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. HAE UK
   b. British Society for Allergy and Clinical Immunology
   c. UKPIN (United Kingdom Primary Immunodeficiency Network)
   d. Takeda UK

4. **Comments on the Appraisal Consultation Document from experts:**
   a. Rachel Annals – patient expert, nominated by HAE UK

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

6. **Evidence Review Group critique of company comments on the ACD**

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

Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

Single Technology Appraisal

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

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and 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.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	BioCryst Pharmaceuticals, Inc.	**Issue 1: The company proposes that berotralstat is used after androgens, but this may prevent some people from accessing treatment.** In the draft ACD, the appraisal committee stated that: *"This population is narrower than that specified in the marketing authorisation and NICE scope. It is also narrower than the intention to treat population of APEX-2 (n=80 in the intention to treat population compared with n=35 in the company's proposed positioning subgroup)…The committee further heard that people under 18 cannot have androgens, but people under 18 are included in the marketing authorisation for berotralstat. The clinical experts stated that supply of androgens in the NHS is inconsistent."* **Company response:** The Company acknowledges the clinical expert comments made during the committee meeting that the supply of androgens in the NHS is inconsistent and that HAE patients under the age of 18 years do not have access to androgens. The Company would like to clarify that the wording in the proposed positioning was intended to include people aged under 18 years, given that they would be "unsuitable" for androgens. In addition, the Company agrees that it would be suboptimal to inadvertently deny access to berotralstat due to androgen supply shortages. The company therefore proposes updating the wording of the berotralstat proposed positioning to: "Adult and adolescent HAE patients aged 12 years or older who experience ≥2 HAE attacks per month and either: • Experience <2 clinically significant HAE attacks per week and are refractory to attenuated androgens, OR • Experience <2 clinically significant HAE attacks per week but cannot be treated with androgens because androgens are unsuitable or unavailable, OR • Experience ≥2 clinically significant attacks per week and are unsuitable for regular injectable prophylaxis with C1-esterase inhibitors or lanadelumab" The intended place of berotralstat in the current treatment pathway is shown in Error! Reference source not found.. **Figure 1: Proposed positioning of berotralstat in the HAE pathway in the UK**	Comment noted. The committee considered your comments at the second meeting; however, it was still concerned that the proposed positioning of berotralstat after androgens use may prevent some people from accessing it. Therefore, it concluded that the larger subgroup including those who may not have used androgens before is more appropriate for decision making. Berotralstat is now recommended regardless of whether or not people have had androgens before. The recommendation in section 1.1 of the FAD has been updated as follows: "Berotralstat is recommended as an option for preventing recurrent attacks of hereditary angioedema in people 12 years and older, only if:

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			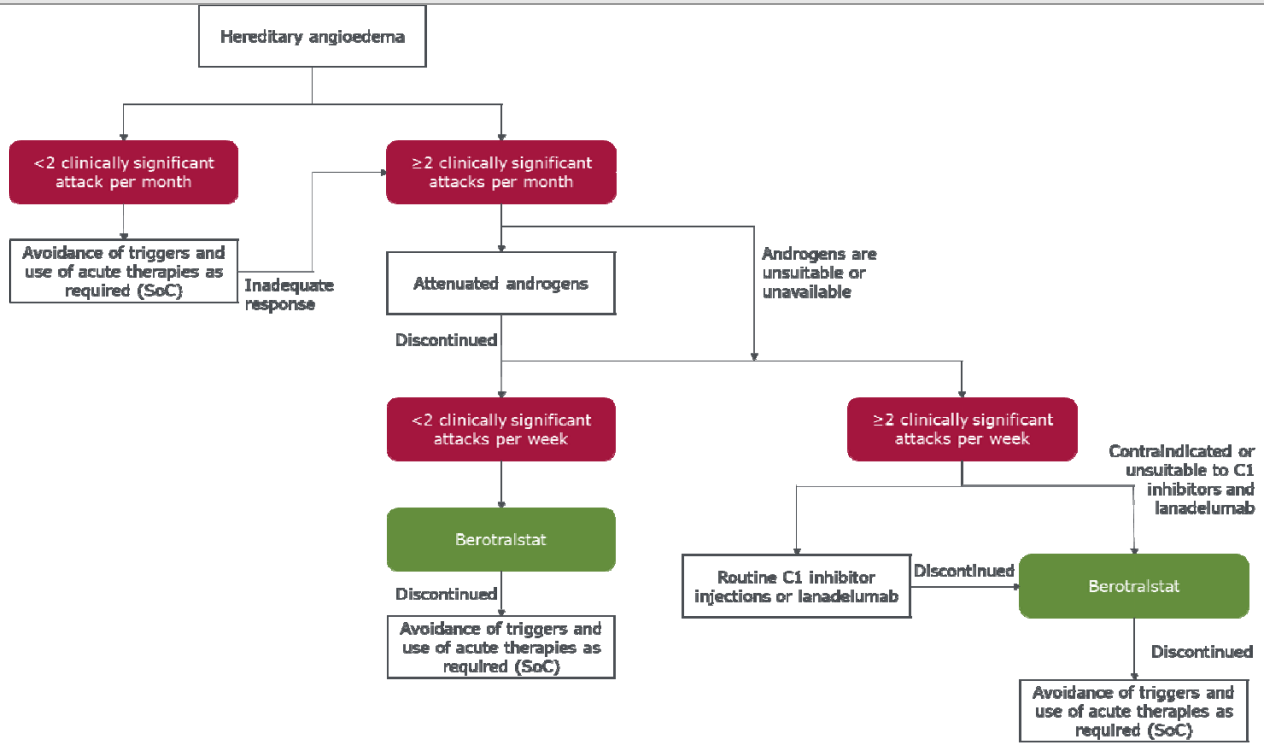 *Abbreviations: HAE, hereditary angioedema; SoC, standard of care; UK = United Kingdom* This subgroup of patients was selected by the Company as it was identified by UK clinical experts at a Delphi panel as the population with the highest unmet need in HAE and represents the patients most likely to be treated with berotralstat in UK clinical practice.[1] It is also the population in which berotralstat is most cost-effective in the Company's original base case, and therefore provides the most efficient use of NHS resources. It should be noted that the revised wording for the positioning has no material impact on the cost-effectiveness analysis, as the revised base case population and associated data remains the same as in the original base case. The company acknowledges, however, that the sample size informing the model is small and has therefore included a scenario analysis in which the model is informed by data from all patients with ≥2 attacks per month (irrespective of androgen use/availability). The results of the Company revised base case in the two different populations is shown in **in the additional data supplementary appendix file.**	• they have at least 2 attacks per month and • it is stopped if the number of attacks per month does not reduce by at least 50% after 3 months." Please also see section 3.1 and section 3.7 of the FAD for a summary of these considerations.

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			References 1. MAP BioPharma Limited. Hereditary Angioedema (HAE) and potential treatments in the UK: Delphi study Final report. Published online 2020.	
2	Company	BioCryst Pharmaceuticals, Inc.	**Issue 2: Clinical evidence suggests berotralstat is more effective than placebo in reducing attack rate, but its effect on attack severity is not known.** In the draft ACD, the appraisal committee stated that: *"They [patient experts] explained that although the reduction in attack rate is a clinically important outcome for people with hereditary angioedema, the reduction in attack severity would be equally important. They noted that if a treatment did not reduce attack rate, but reduced attack severity, they would still value the option to have that treatment. They further highlighted that the hospitalisation of people with hereditary angioedema is often because of attack severity rather than attack rate…The committee recognised that it is important to consider evidence on attack severity as well as attack rate…[The committee] concluded that the clinical evidence suggests berotralstat is more effective than placebo in reducing attack rate, but its effect on attack severity is not known."* **Company response**: The company agrees that attack severity is an important outcome for people with HAE and agrees that a treatment that reduces attack severity and attack rate would be valuable. The original company model base case captures the impact of berotralstat on attack severity using attack location combined with attack duration as objective proxy measures, with data informed by APeX-2 (as outlined below). Additionally, clinicians advised that the need for acute therapy, and the requirement for multiple administrations of acute therapy, also provide measures of attack severity. These proxy measures are objective and rigorous assessments of attack severity. Data from APeX-2 shows that berotralstat reduces attack severity, as measured by attack location. In particular, there was a [redacted] reduction in laryngeal attacks ([redacted]) with berotralstat compared with placebo in APeX-2. Given that laryngeal attacks are potentially life-threatening, berotralstat potentially limits the most severe types of HAE attacks. Similarly, APeX-2 data show that berotralstat reduces attack duration, most notably reducing the mean duration of attack by nearly [redacted] in patients who transitioned from the placebo arm in Part 1 to berotralstat 150mg in Part 2 ([redacted] in placebo Part 1, [redacted] in the same patients transitioning to berotralstat 150mg in Part 2). The impact of berotralstat on attack severity can also be estimated by assessing the number of HAE attacks requiring acute therapy and the rate of acute therapy use per month. In Part 1 of APeX-2, there was a significant [redacted]% reduction in attacks treated with acute therapy in patients treated with berotralstat 150mg compared to placebo ([redacted] vs [redacted] attacks requiring acute therapy per month; [redacted]). In line with this, patients in the berotralstat 150mg arm used [redacted]% fewer doses of acute therapy per month compared to patients in the placebo arm ([redacted] vs [redacted] doses per month; p<[redacted]). Within the economic analysis, the need for actute therapies is captured as part of the cost calculations associated with cost of an attack, and a scenario analysis presented in response to **Issue 9** considers the impact on QoL of including acute therapy administration-related disutilies. Taken together, objective proxies for severity indicate that berotralstat not only reduces HAE attack rate, but also attack severity, compared with placebo.	Comment noted. The committee considered your comments. The committee was dissatisfied that severity data from APeX-2 was not presented and applied in the model. However, it acknowledged that there are limitations with this data. Please see section 3.5 and section 3.10 of the FAD for a summary of these considerations.
3	Company	BioCryst Pharmaceuticals,	**Issue 3: The company's model structure is acceptable for decision making, but the continuation rule may not be appropriate in clinical practice.**	Comment noted. The committee considered

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		Inc.	<u>In the draft ACD, the appraisal committee stated that:</u> *"This [continuation] rule states that people can only continue taking berotralstat if they have a reduction in attack rate of at least 50% compared with baseline by 3 months. However, the committee noted that there was no continuation rule in APEX-2 or the marketing authorisation… The patient experts explained that if people had fewer attacks but did not reach the threshold of a 50% reduction, they would likely want to continue treatment anyway. Also, even if the number of attacks did not decrease, but the severity did, they would consider it beneficial to continue treatment. The committee noted the importance of the patient experts' comments, and was concerned that it would be difficult to implement the continuation rule in clinical practice."* **Company response:** The Company acknowledges that, although there are limitations with continuation rules, they ensure efficient use of NHS resources by targeting treatment to patients who benefit the most while avoiding unnecessary adverse events in patients not benefitting. The Company would like to highlight that a continuation rule for berotralstat has already been incorporated into clinical practice. Berotralstat is available under the Early Access to Medicines Scheme (EAMS), and the Blueteq® criteria requires physicians to tick "I confirm that treatment will be stopped if there has not been a clinically significant reduction in the number of significant angioedema attacks (significant attacks are as defined in the NHS England C1-inhibitor for HAE commissioning policy)[3], observed within 3 months of starting treatment". A continuation rule for berotralstat treatment was deemed appropriate following discussions with UK clinical experts.[1] A Delphi panel of nine UK clinical experts reached a consensus that 3 months after treatment initiation would be a suitable timepoint to assess whether treatment with berotralstat had been successful.[1] Clinicians agreed that a 50% or greater reduction in attack frequency compared to baseline would constitute treatment success.[1] The Company notes that there are precedents for using continuation rules within HAE. The current C1-INH commissioning policy states that: "If treatment is ineffective after two months (defined as a lack of reduction in attack frequency despite optimised treatment) then treatment with prophylactic C1-inhibitor should be discontinued and alternative therapy options considered".[2] Additionally, NICE has previously recommended technologies with continuation rules designed primarily to maximise efficient use of NHS resources, such as pirfenidone for treating idiopathic pulmonary fibrosis.[3] Based on the above, the Company is confident that a continuation rule for berotralstat can be implemented in clinical practice and provides the most efficient use of NHS resources, and is therefore appropriate for the model base case. **References** 1. MAP BioPharma Limited. Hereditary Angioedema (HAE) and potential treatments in the UK: Delphi study Final report. Published online 2020. 2. Specialised Commissioning Team. *Clinical Commissioning Policy: Plasmaderived C1-Esterase Inhibitor for Prophylactic Treatment of Hereditary Angioedema (HAE) Types I and II*. NHS England; 2016:21. https://www.england.nhs.uk/wp-content/uploads/2018/07/Plasma-derived-C1-esterase-inhibitor-for-prophylactic-treatment-of-hereditary-angioesema-types-I-and-II.pdf NICE. 4 Committee discussion | Pirfenidone for treating idiopathic pulmonary fibrosis | Guidance | NICE. NICE. Accessed July 22, 2021. https://www.nice.org.uk/guidance/ta504/chapter/4-Committee-discussion	your comments. It acknowledged the application of a continuation rule for berotralstat in clinical practice through EAMS as well as the continuation rules in place for other treatments for hereditary angioedema through NHS England's commissioning policy on C1-INHs. Therefore, it considered it was appropriate to include a continuation rule in the economic model. The recommendation has been updated to reflect this. Please see section 1.1 and section 3.6 of the FAD for the updated recommendations and a summary of these considerations.
4	Company	BioCryst Pharmaceuticals, Inc.	**Issue 4: It is appropriate to consider analyses from the subgroup who have used androgens before and the larger subgroup who may have not**	Comment noted. The committee considered your comments. The

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			In the draft ACD, the appraisal committee stated that: *"Instead, [the company] provided a scenario analysis using clinical evidence from a larger subgroup (n=57) of people with at least 2 attacks per month who may not have previously used androgens. The ERG agreed with using this larger subgroup because it included more patients than the company's proposed positioning subgroup... the committee concluded that it would consider analyses from the subgroup that has had androgens before as well as the larger subgroup who may not have used androgens before"* **Company response:** The Company acknowledges that there are limitations in the small sample size for the model base case population (patients with ≥2 attacks per month and who have used/are unsuitable for prior androgens) and this may create uncertainties within the cost-effectiveness model. The Company proposed the positioning of berotralstat as it was identified by clinical experts in a Delphi panel as the population with the highest unmet need in HAE and represents the patients most likely to be treated with berotralstat in UK clinical practice.[1] It is also the population in which berotralstat is most cost-effective and therefore provides the most efficient use of NHS resources. As stated in response to **Issue 1**, the Company has proposed some amends to the berotralstat positioning that have no material impact on the data informing the model base case (see **Issue 1** and Error! Reference source not found.). To mitigate Committee concerns over the sample size uncertainty, the Company has included a scenario analysis in which the model is informed by data from all patients with ≥2 attacks per month (irrespective of androgen use/availability). The results of the Company revised base case in the two different populations is shown in **the additional data supplementary appendix file** and, crucially, confirms that berotralstat is cost-effective in both populations. **References** 1. MAP BioPharma Limited. Hereditary Angioedema (HAE) and potential treatments in the UK: Delphi study Final report. Published online 2020.	recommendation has now been updated. See response to comment 1 above and section 3.1 and section 3.7 of the FAD for a summary of these considerations.
5	Company	BioCryst Pharmaceuticals, Inc.	**Issue 5: It is uncertain how much berotralstat reduces attacks compared with standard care beyond the trial follow up period.** In the draft ACD, the appraisal committee stated that: *"…in its revised base case, the company assumed a 0% reduction in attack rate for the standard care arm to be carried forward beyond 6 months in the model. This was different from the ERG's suggested approach to carry forward the average attack rate reduction between months 0 and 6. The ERG explained that the company's approach only removed the placebo effect from the standard care arm. But it suggested that some placebo effect is also likely in the berotralstat arm as well. The committee suggested it may be more appropriate to adjust the average percentage reduction in attack rate in the berotralstat arm carried forward beyond the observed trial period, using the size of placebo effect seen in the standard care arm."* **Company response:** The Company accepts that there are limitations in all approaches to the extrapolation of attack	Comment noted. The committee considered your comments. However, the committee considered that the company's revised approach inconsistent and likely to favour the treatment effect in the berotralstat arm. Therefore, it concluded that the extrapolation of attack rate reduction that applies the placebo effect

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			rate data for the SOC arm, given that there are only 6 months of data in the placebo arm in APeX-2. As highlighted during technical engagement, clinical experts at an advisory board stated that they believed that placebo patients in APeX-2 may have experienced a placebo effect, noting that a similar pattern in attack rates for placebo patients was observed in other studies in HAE.[1] Experts stated that the placebo effect may be driven by reduced anxiety and stress and is likely to taper off after several months, once the patient suspects that they are receiving placebo and not active treatment.[1] The high monthly attack rate in the placebo arm at Month 6 of APeX-2 confirms that the placebo effect may have worn off by Month 6. In contrast, patients in the berotralstat arm experience a consistent and durable decrease in the mean monthly attack rate compared with baseline beyond Month 6. In recently published data from Kiani et al (2021)[2], APeX-2 patients treated with berotralstat 150mg showed a durable reduction from baseline in the HAE attack rate per month across 96 weeks.[2] In fact, the magnitude of benefit with berotralstat increased over time, with mean monthly attack rate generally decreasing steadily from Month 1 through to Month 24. These 24-month data are now included in the model base case and give confidence that the berotralstat treatment effect is not related to a placebo effect. **Please refer to the additional data supplementary appendix file to view the 96-week data.** In contrast, clinical experts at an advisory board expected the placebo effect with placebo to taper off after several months.[1] APeX-2 was a double-blinded trial in which patients may have believed that they were randomised to receive berotralstat when in actuality were treated with placebo. Given the role of stress and anxiety in driving attack rates in HAE, patient belief of being on active treatment may have led to a reduction in their stress and anxiety, which is reflected in the short-term reduction in attack rate in the placebo arm of APeX-2. Furthermore, as noted by clinical experts at an advisory board,[1] patients typically experience an improved level of overall care in a clinical trial than in clinical practice, which may have influenced the reduction in attack rate for placebo patients despite the lack of active prophylactic therapy. Based on the above, it is implausible to expect that HAE attacks would be reduced over a 96-week period in the placebo arm of APeX-2. Based on the above, and acknowledging the Committee concerns regarding the SOC extrapolations, the Company has revised the model base case extrapolations to a more conservative approach than in the original model base case. In the revised Company base case, rather than using the pooled baseline attack rate for the SOC extrapolations, the placebo attack rate is gradually tapered from months 6-12 to reflect the clinical expert opinion that the placebo effect would taper off after several months.[1] The revised model approach to extrapolating the berotralstat and SOC arms is as follows: • **Berotralstat:** uses the observed APeX-2 study data for berotralstat 150mg up to the last observation (Month 24), after which the mean monthly attack rate from month 4 to 24 is applied over the remainder of the model time horizon. • **SOC:** uses the observed APeX-2 study data for placebo up to the last observation (Month 6). At Month 7, the mean monthly attack rate over months 1-6 is applied and is then tapered to the pooled baseline attack rate in a linear fashion in months 7-12. From Month 12 onwards, the pooled baseline attack rate is applied for the SOC arm. The Company is confident that the inclusion of 96-week data for berotralstat 150mg, and tapering of the placebo effect for SOC, represents the most realistic and clinically plausible approach to extrapolating the beyond the APeX-2 trial	consistently across treatment arms is more appropriate. Please see section 3.8 of the FAD for a summary of these considerations.

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			follow-up period and is a more conservative approach than the original base case. **Please refer to the additional data supplementary appendix file to view the revised base case model results.** **References** 1. *UK Advisory Board. BioCryst Data on File. 29 March 2021*. 2. Kiani S. Durable Reduction in Hereditary Angioedema (HAE) Attack Rates with Berotralstat Over 24 Months: Results from the Phase 3 APeX-2 Study. Presentation presented at the: EAACI Digital Congress; 2021; Virtual.	
6	Company	BioCryst Pharmaceuticals, Inc.	**Issue 6: Additional analysis using utility values that reflect attack severity as well as attack rate reduction would be preferable.** In the draft ACD, the appraisal committee stated that: *"The committee was concerned that using utility values directly from APEX-2 may not adequately capture the effect of attacks on health-related quality of life and do not reflect the effect of attack severity. But it noted that the latter was likely to apply to the utility values from Nordenfelt et al. too. The committee concluded that additional analysis using utility values that reflect attack severity as well as attack rate reduction would be preferable."* **Company response:** The company agrees that attack severity is an important outcome for people with HAE and agrees that a treatment that reduces attack severity and attack rate would be valuable. As outlined in response to **Issue 2**, the original Company model base case captures the impact of berotralstat on attack severity using attack location combined with attack duration as proxies and showed that berotralstat reduces attack severity compared with placebo. Berotralstat also reduces the need for acute therapies to manage attacks, further confirming its impact on severity, and this is captured in the model cost calculations. These proxy measures are an objective and rigorous assessment of attack severity in the absence of other objective measures from APeX-2. In the model, a single disutility value (based on data from Nordenfelt et al. 2014)[1] is applied for the duration of each HAE attack. Given that attack duration is used as a proxy for severity, the utility values in part reflect both attack severity as well as attack rate. The Company considers this to be a conservative approach and may not fully capture the value of berotralstat in reducing attack severity compared with placebo. In an attempt to factor in the quality of life implications of berotralstat reducing the need for acute therapies compared to standard of care (a proxy for attack severity), a scenario is considered in which an administration disutility is applied when a patient requires injectable acute therapy. Further details are presented in the response to **Issue 9**. **References** 1. Nordenfelt P, Dawson S, Wahlgren C-F, Lindfors A, Mallbris L, Björkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. Allergy Asthma Proc. 2014;35(2):185-190. doi:10.2500/aap.2014.35.3738	Comment noted. The committee considered your comments. Although the committee acknowledged that the duration of attack as a proxy of attack severity is reflected in the utility estimates, it noted that there was little difference in duration of attacks between treatments. It concluded that analysis using utility values that reflect attack severity as well as attack rate reduction would have been preferable. Please see section 3.5 and section 3.10 of the FAD for a summary of these considerations.
7	Company	BioCryst Pharmaceuticals,	**Issue 7: It is not appropriate to include health-related quality of life effects for carers in the base case.**	Comment noted. The committee considered

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		Inc.	<u>In the draft ACD, the appraisal committee stated that:</u> *"…the committee noted that although many diseases and conditions may adversely affect carers, few technology appraisals model this. For example, carer disutility was not included in a previous appraisal in this disease area (see NICE technology appraisal guidance on lanadelumab)…the committee concluded that it was not appropriate to include health-related quality of life effects for carers in the base case."* **Company response:** The Company acknowledges that other HAE appraisals do not apply a caregiver disutility. However, it is within the remit of NICE to consider caregiver burden, with the reference case stating that the following should be considered: "all direct health effects, whether for patients or, when relevant, carers". Caregivers of patients with HAE experience considerable burden from time spent offering both physical and emotional support, as well as shared anxiety over attacks.[2,3] HAE attacks can be fatal and many are very disabling, with patients confined to bed for hours or days, or left without use of their limbs.[4] Due to the hereditary nature of the disease, many carers may also be HAE patients, who not only fear for their own attacks, but also the attacks of those to whom they are providing care. HAE attacks can end in death[4] and patients with HAE may have relatives who have died from an attack. This fear of death was highlighted by clinical experts at an advisory board, who agreed it was common and a key component of attack-related anxiety.[1] In the Company economic analysis, the caregiver disutility of [redacted], while substantial, is only applied when patients are experiencing an attack. Additionally, caregiver disutility is only applied to 52.4% of attacks to align with the proportion of patients who reported receiving assistance from a caregiver during their last attack in Aygören-Pürsün *et al.* (2014).[2] Taken together, therefore, the caregiver disutility is only applied for an average of [redacted] days per monthly cycle for berotralstat ([redacted]% of time per month) and [redacted] days per monthly cycle for SOC ([redacted]% of time per month). Given the anxiety and stress among both patients with HAE and their caregivers, the Company is confident that these assumptions are conservative. For example, an alternative approach could be to assume that all attacks requiring acute therapy need caregiver support. Using this assumption, a caregiver disutility would be applied to [redacted]% of attacks with SOC and [redacted]% of attacks with berotralstat. This would mean that caregiver disutility would have a much greater influence on the analysis when compared with the 52.4%[2] of attacks used in the base case model. Despite the clear and documented caregiver burden of HAE, the Company accepts that previous HAE appraisals did not consider caregiver burden and has amended the base case analysis to remove carer disutility. The Company has included a scenario analysis in which carer disutility is included in the economic model. In both scenarios, berotralst is dominant versus standard of care. **References** 1. *UK Advisory Board. BioCryst Data on File. 29 March 2021*. 2. Aygören-Pürsün E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. *Orphanet J Rare Dis*. 2014;9:99. doi:10.1186/1750-1172-9-99	your comments; however, there was no clear evidence to suggest that the utility gains for carers associated with berotralstat use would be greater than those associated with displaced treatments. Please see section 3.11 of the FAD for a summary of these considerations.

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			3. HAE international, Copenhagen Economics. HEREDITARY ANGIOEDEMA IN THE UK, Survey and model results. Published online October 2020. 4. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol*. 2012;130(3):692-697. doi:10.1016/j.jaci.2012.05.055	
8	Company	BioCryst Pharmaceuticals, Inc.	**Issue 8: The cost-effectiveness estimates are highly uncertain, and some are substantially higher than £20,000 per QALY gained.** In the draft ACD, the appraisal committee stated that: *"The cost-effectiveness estimates were substantially uncertain because of: uncertainty about the attack rate reduction beyond the trial follow-up…the small patient numbers from APeX-2…the acceptability of the treatment continuation rule in clinical practice…attack severity not reflected in the utility estimate. For some clinically plausible scenarios the ICERs were substantially higher than £20,000 per quality-adjusted life year (QALY) gained. So berotralstat cannot be recommended."* **Company response**: The Company acknowledges the issues raised by the Committee and has therefore provided a revised base case in **the additional data supplementary appendix** to reduce uncertainty. The revised base case demonstrates that berotralstat is dominant compared with SOC in both the ≥2 attacks population and the prior androgen population. In developing the revised base case ICER, the Company has acknowledged and/or directly addressed all of the key concerns raised by the committee regarding the ICER uncertainty: • **Uncertainty about attack rate extrapolation:** See response to Issue 5. • **Small patient numbers in APeX-2:** See response to Issues 1 and Issue 4. • **Acceptability of continuation rule in clinical practice:** See response to Issue 3. • **Inclusion of attack severity:** See response to Issue 2 and Issue 6. The Company has also attempted to reduce some of the long-term uncertainty by including 96-week data from APeX-2 for patients treated with berotralstat 150mg. In addition to this, the Company has access to preliminary data on patients using berotralstat in real-world clinical practice in the UK, as part of the Early Access to Medicines Scheme (EAMS). A summary of key findings from the EAMS data is shown in the **additional data supplementary appendix file**.	Comment noted. The committee considered your comments. Please see responses to comments 1 to 6 above. The recommendation has now been updated. Please see section 1.1 and section 3.12 of the FAD for the updated recommendation and for a summary of the cost-effectiveness considerations.
9	Company	BioCryst Pharmaceuticals, Inc.	**Issue 9: Berotralstat is an innovative prophylactic treatment for recurrent attacks of hereditary angioedema.** In the draft ACD, the appraisal committee stated that: *"The committee considered berotralstat to be innovative because it would be the first licensed oral prophylactic treatment option for people with recurrent attacks of hereditary angioedema. This would mean people would have*	Comment noted. The committee considered your comments. Please see section 3.14 of the FAD for a summary of these considerations.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			access to medicine that is more convenient than injectables…The committee concluded that berotralstat is an innovative prophylactic treatment for recurrent attacks of hereditary angioedema, but all relevant benefits are reflected in the cost-effectiveness estimates." **Company response**: The Company was pleased to note that the Committee acknowledged the high unmet need in HAE and that the committee considers berotralstat to be innovative and urges the Committee to take these considerations into account in their decision-making. The Company agrees with the Committee that HAE can be a severe and debilitating condition and that there is a lack of effective prophylactic options. The urgent need for effective prophylactic therapies should be taken into consideration when evaluating the cost-effectiveness of berotralstat. The Company also agrees with the Committee that berotralstat is innovative and offers the first and only licenced oral prophylactic treatment option for people with recurrent attacks of HAE. As described in the response to **Issue 2**, APeX-2 trial data show that berotralstat reduces the need for acute therapy compared with placebo. Given that acute therapies are administered via subcutaneous or intravenous injections, the Company considers the oral mode of administration to be an important additional benefit of berotralstat. In fact, a report from Holko et al (2018)[1] demonstrates that oral therapies are associated with a utility benefit of 0.164 and 0.147 over intravenous or subcutaneous therapies, respectively, in patients with inflammatory bowel disease.[1] Similarly, a study on treatment satisfaction in HAE patients found that 50% of patients prefer non-invasive methods of administration, while another study reported that 62% of respondents who used a peripheral vein to administer treatment reported difficulty finding a vein or getting the infusion to work properly.[2,3] Fear of needles, injection site reactions, hard-to-find veins, and the increased burden on the NHS for treatment administration, are all problems that could be addressed by the reduced HAE attack rate and need for acute therapy in patients who use berotralstat versus SOC. While the revised model base case conservatively excludes any potential benefits of berotralstat's mode of administration, the Company has provided a scenario in which administration disutilites are applied for attacks requiring acute therapy and depending on the acute therapy received, using data from Holko et al (2018).[1] **Please refer to the additional data supplementary appendix file to view the revised base case and scenario model results** and shows that berotralstat is dominant in both scenarios. **References** 1. Holko P, Kawalec P, Mossakowska M. Quality of life related to oral, subcutaneous, and intravenous biologic treatment of inflammatory bowel disease: a time trade-off study. Eur J Gastroenterol Hepatol. 2018;30(2):174-180. doi:10.1097/MEG.0000000000001031 2. Riedl MA, Banerji A, Busse PJ, et al. Patient satisfaction and experience with intravenously administered C1-inhibitor concentrates in the United States. Annals of Allergy, Asthma & Immunology. 2017;119(1):59-64. doi:10.1016/j.anai.2017.05.017 3. Jose J, Lehman EB, Craig T. Evaluating satisfaction of patients with hereditary angioedema with their past and present treatments: Implications for future therapies. Allergy and Asthma Proceedings. 2018;39(1):74-80.	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			doi:10.2500/aap.2018.39.4095	
10	Professional group	British Society of Allergy and Clinical Immunology	Stopping therapy if ineffective is raised as possibly not clinically appropriate in practice; it is unlikely the technology would be continued if not effective; it would be reasonable to consider normal practice to review stable patients every 6 months, and those requiring a new therapy / intervention earlier than this. When commencing prophylaxis patients will generally be reviewed every 6-12 weeks. If prophylaxis if not effective at the recommended dose then it is likely that the treatment would be stopped at that stage. This would be normal practice when considering prophylaxis with attenuated androgens, they would be stopped if not effective. Overall a 50% reduction in disease would be a reasonable assumption for effectiveness and would support ongoing use in those with the greatest benefit	Comment noted. The committee considered your comments. The recommendation has now been updated. Please see response to comment 3 above and section 3.6 of the FAD for a summary of these considerations. Please see section 1.1 of the FAD for updated the recommendation.
11	Professional group	British Society of Allergy and Clinical Immunology	It is important to highlight that HAE as a condition can be significantly impacted by psychological state. Although the disease will often be stable when averaged over life, fluctuations are common related to life factors. Flares / increase in activity can often be seen at times of marked stress, and improvement when there is less stress / enhanced confidence. This could exacerbate the placebo effect of being in a clinical trial when compared to other diseases – and this might impact on the modelling of the placebo effect in the control arm. This could explain the initial reduction in disease activity following enrolment and then the return / overshoot of baseline attack rate seen in the placebo group	Comment noted. Please see response to comment 5 above and section 3.8 of the FAD for a summary of these considerations.
12	Professional group	British Society of Allergy and Clinical Immunology	The selection of the proposed treatment group being those with 2 or more attacks is reasonably based as these are likely to be the patients with moderate to severe disease and most likely to benefit. Patients with attacks less frequently are generally less inclined to take regular or preventative therapy to avoid attacks. Certainly, when considering attenuated androgen prophylaxis most patients with less frequent attacks will not commence prophylaxis. Although it would be an advantage to be able to offer all patients all treatment options it is already a reality in this condition that there are criteria for access and being able to offer this technology to patients that currently do not have a suitable other option would be a real advantage. In other intermittent conditions for example spontaneous urticaria and angioedema, often patients will only take a prophylactic therapy if events are more frequent than 1-2 times monthly	Comment noted. The recommendation has been updated. Please see section 1.1 of the FAD.
13	Professional group	British Society of Allergy and Clinical Immunology	Although severity assessment and inclusion in treatment decisions may be an advantage in HAE there are currently no suitable and easy to use severity tools that are in widespread clinical use. Perhaps it is aspirational to include this aspect – arguably ideal, but maybe not practical currently in routine clinical practice	Comment noted.
14	Patient/carer group	HAE UK (Patient support and advocacy charity for people and families affected by Hereditary Angioedema)	HAE UK is very concerned that the only currently licensed form of prophylaxis that is an oral formulation rather than an injectable will not be available to patients in the UK. Oral presentation is of great benefit to patients who have poor venous access or are not otherwise able to inject, or who may be in a situation where injecting is impractical	Comment noted. The recommendation has been updated. Please see section 1.1 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
15	Patient/carer group	HAE UK (Patient support and advocacy charity for people and families affected by Hereditary Angioedema)	Attacks of HAE (if left untreated) are of long duration, sometimes 2 to 3 days before complete resolution, leaving patients exhausted and debilitated. This is not always fully appreciated. Some patients are managed by a carer (usually a family member) who administers injections and carries out other tasks whilst the patient is undergoing an attack. The condition therefore affects the life and livelihood of more than one person.	Comment noted. The committee considered your comments. Please see response to comment 7 above and section 3.11 of the FAD for a summary of these considerations.
16	Patient/carer group	HAE UK (Patient support and advocacy charity for people and families affected by Hereditary Angioedema)	The current positioning is of advantage to allow prophylaxis to patients who do not currently qualify for injectable prophylactic treatment (C1-INH or lanadelumab) and yet still have recourse to frequent and extensive use of C1-INH or icatibant in order to manage attacks of Hereditary Angioedema (HAE). Prophylaxis for these patients will reduce the burden of the condition to patients, the NHS and carers.	Comment noted. The recommendation has been updated. Please see section 1.1 of the FAD.
17	Patient/carer group	HAE UK (Patient support and advocacy charity for people and families affected by Hereditary Angioedema)	HAE UK supports the discontinuation of the use of berotralstat if there is inadequate response.	Comment noted. The committee considered your comments. The recommendation has been updated. Please see response to comment 3 above and section 3.6 of the FAD for a summary of these considerations. Please see section 1.1 of the FAD for the updated recommendation.
18	Patient/carer groups	HAE UK (Patient support and advocacy charity for people and families affected by Hereditary Angioedema)	As with all forms of prophylaxis it would not be reasonable to expect this to be a life-long treatment, but may be very appropriate used, for example, to see a young person through school exam periods and university/college. Otherwise, attacks of HAE may affect their exam performance, course work and ultimate life chances.	Comment noted.
19	Patient/carer group	HAE UK (support charity for people with hereditary angioedema)	My attacks would be very long (3 or so days) if untreated. This would mean I couldn't work or manage day-to-day activities and I would need to reply on support from family or friends for care of my daughter. This shows that it is not just the patient who is affected, but it has a direct impact on my daughter's wellbeing and my need for support from others. I think this is an important point to consider.	Comment noted. The committee considered your comments. Please see response to comment 7 above and section 3.11 of the FAD for a summary

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				of these considerations.
20	Patient/carer group	HAE UK (support charity for people with hereditary angioedema)	I firmly believe patients should have a choice as to which medication they choose to take. There is currently no licensed oral prophylactic medication for patients, meaning those with poor vein access or those with a fear of needles, are limited in their choices and would rely more on carers or hospital staff to help with administration. Stress is a big trigger for many peoples attacks and having no prophylactic medication can cause unnecessary anxiety and stress about an attack occurring.	Comment noted. The recommendation has now been updated. Please see section 1.1 of the FAD for the updated recommendation.
21	Patient/carer group	HAE UK (support charity for people with hereditary angioedema)	I would support the discontinuation of Berotralstat if I didn't receive a good response from treatment. I feel a 3 month trial period is sufficient to know whether it would work for me.	Comment noted. The committee considered your comments. The recommendation has been updated. Please see response to comment 3 above and section 3.6 of the FAD for a summary of these considerations. Please see section 1.1 of the FAD for the updated recommendation.
22	Patient/carer group	HAE UK (support charity for people with hereditary angioedema)	Currently many patients do not fit the criteria for prophylactic medication. Berotralstat would offer this option to patients who suffer severe and debilitating attacks, often requiring hospital treatment, who currently are unable to have prophylactic treatment.	Comment noted. The recommendation has been updated. Please see section 1.1 of the FAD.
23	Comparator	Takeda UK Limited	We welcome increased treatment options for hereditary angioedema patients and clinicians. We believe that the primary aim of treatment should be attack freedom when achievable and aligned to individual patients' needs and wishes. We agree with the Committee's view that a reduction in the severity of the attacks is important, however note that all attacks can affect daily life for patients living with hereditary angioedema. A German study by Bork *et al*. (Mayo Clin Proc. 2000 Apr;75(4):349-54) highlighted the risks associated with laryngeal oedema attacks in patients with hereditary angioedema. The study included a retrospective survey of 58 patients, of which 23 died due to asphyxiation (40%). This study highlights that laryngeal oedema attacks may be fatal in patients with frequent attacks as well as those with rare episodes of swelling. In addition, as acknowledged by the company, the measurement of attack severity can be subjective. Therefore, whilst severity of attacks is important to consider, the primary goal of treatment should be to reduce the total number of attacks so that patients can, wherever possible, maintain an attack-free life. We believe that informed patient choice and clinical opinion should dictate treatment decisions.	Comment noted. The committee considered your comments. Please see response to comment 2 above and section 3.5 and section 3.10 of the FAD for a summary of these considerations.
24	Professional group	[UKPIN]	If there was a continuation rule, this would likely be implemented in clinical practice. There is precedent for continuation rules already in the C1 inhibitor prophylaxis commissioning policy for HAE, as well as in the use of omalizumab for treatment of chronic spontaneous urticaria (which is a different condition, but also has angioedema as one its clinical features).	Comment noted. The committee considered your comments. The recommendation has

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				been updated. Please see response to comment 3 above and section 3.6 of the FAD for a summary of these considerations. Please see section 1.1 of the FAD for the updated recommendation.
25	Professional group	[UKPIN]	In section 3.5, it is stated that effect on attack severity is not known – however, surrogate measures like attack duration and amount of rescue medication usage can be used as measures of severity – it would be useful to know if these were looked at when considering the effect of berotralstat on attack severity.	Comment noted. The committee considered your comments. The recommendation has now been updated. Please see response to comment 2 above and section 3.5 of the FAD for a summary of these considerations. Please see section 1.1 of the FAD for the updated recommendation.
26	Other (web comment)	Barts Health NHS Trust, Department of Immunology	• Has all of the relevant evidence been taken into account? My comments are informed by my experience of being the lead for HAE at Barts Health NHS Trust where the largest UK cohort of adults and children with HAE cared for. At Barts, we performed the clinical trials for Berotralstat and currently are treating 13 patients with Berotralstat on the EAMS scheme. I have been the principle and chief investigator for the Berotralstat clinical trials and other HAE drugs such as Lanadelumab or KVD-900. I am the senior author for the APEX-2 (48- weeks Berotralstat) and presented the 96- weeks data for Berotralstat in the European Academy of Allergy and Clinical Immunology (EAACI) congress 2021. Real wold evidence (RWE) has been accumulating since the Early Access to Medicines Scheme for Berotralstat in February 2021. Approximately 100 patients in the UK are on Berotralstat through EAMS. We are collecting data on these patients through the UK HAE network. This could provide relevant evidence but are not included in this consultation.	Comment noted.
27	Other (web comment)	Barts Health NHS Trust, Department of Immunology	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No comments.	Comment noted.
28	Other (web comment)	Barts Health NHS Trust,	• Are the recommendations sound and a suitable basis for guidance to the NHS?	Comment noted.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
		Department of Immunology	No comments	
29	Other (web comment)	Barts Health NHS Trust, Department of Immunology	• 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? No comments.	Comment noted.
30	Other (web comment)	Barts Health NHS Trust, Department of Immunology	• Section 1 APEX-2 studied the effect of Berotrastat over a 48 weeks' period. Compared to other clinical trials for HAE, APEX-2 could be considered as a long trial. HELP study for Lanadelumab was conducted over a 26 weeks' period. The APEX-S study extended the use of Medication to 96 weeks demonstrating durability of the efficacy and a very good safety profile over the 96 weeks of the study. In our cohort of 13 patients who are being treated with Berotralstat we continue to observe the reduction in attack frequency and the number of attacks that require treatment (i.e reduction in attack severity) Since HAE is a rare disease, inevitably the number of participants in clinical trials are low and this is the case for all HAE trials. The effect of a drug on attack location and severity is indeed important and it was taken into account in the APEX-2 study as the number of attacks requiring treatment were measured which is a surrogate for attack severity and location. Please note that all above-neck attacks are considered to be more dangerous and should be treated.	Comment noted. The committee considered your comments.
31	Other (web comment)	Barts Health NHS Trust, Department of Immunology	• Section 3.2 - The company proposes that berotralstat is used after androgens, but this may prevent some people from accessing treatment There is a considerable number of patients for whom prophylaxis is indicated but fall in between the group who are eligible to receive prophylactic C1- Inhibitor replacement therapy or Lanadelumab, and the group for whom prophylaxis is not indicate. These patients have no other choice apart from attenuated androgens (AAs) but AAs are not appropriate for all the members of this cohort. Some patients may not wish to have androgens as they find the side effect profile unacceptable or AAs are contraindicated for them in which case their only choice of prophylaxis is Berotralstat provided they has access to it.	Comment noted. The recommendation has been updated. Please see section 1.1 of the FAD.
32	Other (web comment)	Barts Health NHS Trust, Department of Immunology	• Section 3.6 - The company's model structure is acceptable for decision making, but the continuation rule may not be appropriate in clinical practice Attack frequency is a useful measure of disease control and is an indicator of attack severity. Patients with can have flares of disease during which attack severity and frequency increases. Reduction in attack frequency often occurs along with a reduction in attack severity. The commissioning guidelines for the use of C1-Inhibitor replacement or Lanadelumab recommend adjustment of frequency or dose of medication based on attack frequency. It is important to note that a reduction in attack frequency that is less than 50% can be significant, if there are no other	Comment noted. The committee considered your comments. The recommendation has now been updated. Please see response to comment 3 above and section 3.6 of the FAD for

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			treatments that could achieve a better outcome. The decision of starting or stopping prophylaxis, in practice, is made jointly between a patient and a clinician. The primary factor that influences this decision is patient quality of life (QoL). The final decision is based on a combination of benefits, side effects, inconvenience of use, and whether any other alternative drugs exist that may provide better treatment. In a survey of UK clinical immunologists that I also took part, the consensus was that the clinicians would consider changing prophylaxis if there was not a >50% reduction in attack rate after 3 months. This is a useful cut-off for the clinician to reassess the patient and decide together with the patient on continuation of the treatment. However if , despite a <50% reduction in attack rate, the patient reports a degree of improvement in QoL that could not be obtained by switching to any other available prophylactic medication, in practice, the current treatment would continue based on a patient-centred joint decision. The improvement in QoL could come from a reduction in attack severity, number of attacks requiring acute treatment or change in the location of swellings that could result in a reduction in the risk of asphyxiation. In addition, having a cut-off point would also allow an opportunity to reassess patients for emergence of new factors contributing to HAE flares. e.g. are there underlying psychological or physical precipitating factors at this point of time which are contributing to the inadequate response to prophylaxis. Addressing these underlying factors could increase the magnitude of the response to prophylaxis. Please note that it is now accepted knowledge that HAE severity changes with physiological and psychological changes such as for instance colonisation with H pylori or going through a psychologically stressful period of time.	a summary of these considerations. Please see section 1.1 of the FAD for the updated recommendation.
33	Other (web comment)	Barts Health NHS Trust, Department of Immunology	• Section 3.8 - It is uncertain how much berotralstat reduces attacks compared with standard care beyond the trial follow up period Our real world experience at Bart Health with the 3 patients from the APEX-S study who have continued with medication through EAMS who have been on Berotralstat for >96 weeks now and patients who have been on EAMS from February 2021, shows that similarly to Lanadelumab in HELP-OLE studies, there is a progressive reduction in attack rates after a few months of treatment. This is interesting as both these medications target the same enzyme (Kallikrein). Clinically it appears that the contact system may reach a different level of equilibrium with time which results in lower frequency of attacks. From our RWE the disease in patients who do respond to Berotralstat seems to become progressively more stable wit time.	Comment noted.
34	Other (Web comment)	Not known	• Has all of the relevant evidence been taken into account? The appropriate clinical trial evidence has been considered. The committee comments on the trial size, however, this would be commensurate with trials in rare diseases, where treatable populations are small and ability to recruit and randomise is challenging. The trials are consistent with other HAE therapeutics that have gone through the licensing process.	Comment noted.
35	Other (web comment)	Not known	• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? The clinical efficacy data from the trials is evident, with a significant reduction in attack frequency and no concrete	Comment noted. The recommendation has been updated. Please

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			data, but as a clinician with real life experience, I would note that patients attack severity has also diminished, which is a highly important factor in considering therapeutic options. The cost effectiveness is partly based on withdrawal if therapy is not effective for that individual. This would be routine counselling for a new high-cost therapy. The comment re: severity needs consideration - a patient who had ongoing minor, non treatable attacks of HAE, who had been getting severe life threatening episodes would be considered a treatment response and should continue, but patients with no significant alteration in attack frequency or severity should not continue therapy and this would be standard practice with the currently available options, mainly due to the toxicities of e.g. androgens which would not be continued if the patient was non-responsive. There should not therefore be a concern that individuals who do not benefit from the medicine are discontinued, since this would be good practice. Given the committees concern on the practicality of using a 50% reduction threshold to determine continuation of therapy, perhaps a clinically effective model (reduction in frequency and/or severity) would be appropriate, but clear guidance on discontinuation for sub-optimal response should be made. I would query the assumptions or the basis of it for treatment associated costs (acute therapy). The experience of androgens and tranexamic acid in treating patients with HAE is that when effective they reduce the severity and/or frequency of attacks. Treatment of acute attacks tends to diminish because there are fewer severe treatable attacks and milder attacks tend to resolve more quickly and are less likely to require rescue second therapy/re-treatment, which would reduce the cost of acute therapy. With regards carer disutility, I would like to see a measure included. I care for a cohort of children at a children's hospital. Parents will have to take time off work or study and care for a sick child, with a recurring unpredictable disorder. The impact on carers is both economically and socially significant and it is appropriate to consider the impact of the therapy on a family. In terms of clinical effectiveness and durability, my experience through the EAMS scheme has been that the efficacy of the therapy increases over time (progressively better control); I accept that this isn't obvious from the pivotal study, but would hope that the company can produce data that shows increasing efficacy over time. Even if the data is not available, those patients who lost benefit, would therefore fall under the failed efficacy clause and treatment would be withdrawn.	see section 1.1 of the FAD.
36	Other (web comment)	Not known	• Are the recommendations sound and a suitable basis for guidance to the NHS? The recommendations as a prescribing clinician who is responsible for the care of children as well as adults with HAE are disappointing. Trials in HAE are small because it is a rare disease and so by definition if they meeting the criteria set out by regulators in the USA and Europe for marketing authorisation and have appropriate statistical validity, they should be sufficient to make a decision for the NHS on the validity of commissioning. The recommendations do not seem to take into account that under the heading "inappropriate for androgen therapy" would include patients who are 12-18 years of age who are not appropriate to receive hormonal therapy. This falls within the remit of the marketing authority and this group of patients do not have a viable alternative therapy for prophylaxis. Tranexamic acid is used "off-label" in this group, with low efficacy and is rejected by some families because of the perceived risk of thrombosis. Androgens and progestogens are either medically inappropriate in this age group or declined because of the side effect profile by carers. The guidance at point 3.2 appears to be flawed, since, androgens are not suitable for patients who cannot medically be prescribed them or for whom the side effect profile is unacceptable, this falls within the proposed guidance that Berotralstat would be offered to those for whom androgens are inappropriate, I cannot therefore foresee a population group that would be denied therapy on this basis.	Comment noted. The recommendation has been updated. Please see section 1.1 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
37	Other (web comment)	Not known	• 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? I would note that children will be specifically disadvantaged if this therapy is not made available, the discrimination would be indirect, but since by virtue of age they are nearly always ineligible for androgens, and there are no licensed oral prophylactic therapies a negative decision would explicitly disadvantage/discriminate against this group where limited options may be available for older patients.	Comment noted. The recommendation has been updated. Please see section 1.1 of the FAD.

NICE National Institute for Health and Care Excellence

Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]
Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 28 July 2021. Please submit via NICE Docs.

	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):	**BioCryst Pharmaceuticals, Inc.**
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.
Example 1	We are concerned that this recommendation may imply that ……..

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]
Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 28 July 2021. Please submit via NICE Docs.

1	**Issue 1: The company proposes that berotralstat is used after androgens, but this may prevent some people from accessing treatment.** In the draft ACD, the appraisal committee stated that: *"This population is narrower than that specified in the marketing authorisation and NICE scope. It is also narrower than the intention to treat population of APEX-2 (n=80 in the intention to treat population compared with n=35 in the company's proposed positioning subgroup)…The committee further heard that people under 18 cannot have androgens, but people under 18 are included in the marketing authorisation for berotralstat. The clinical experts stated that supply of androgens in the NHS is inconsistent."* **Company response:** The Company acknowledges the clinical expert comments made during the committee meeting that the supply of androgens in the NHS is inconsistent and that HAE patients under the age of 18 years do not have access to androgens. The Company would like to clarify that the wording in the proposed positioning was intended to include people aged under 18 years, given that they would be "unsuitable" for androgens. In addition, the Company agrees that it would be suboptimal to inadvertently deny access to berotralstat due to androgen supply shortages. The company therefore proposes updating the wording of the berotralstat proposed positioning to: "Adult and adolescent HAE patients aged 12 years or older who experience ≥2 HAE attacks per month and either: • Experience <2 clinically significant HAE attacks per week and are refractory to attenuated androgens, OR • Experience <2 clinically significant HAE attacks per week but cannot be treated with androgens because androgens are unsuitable or unavailable, OR • Experience ≥2 clinically significant attacks per week and are unsuitable for regular injectable prophylaxis with C1-esterase inhibitors or lanadelumab" The intended place of berotralstat in the current treatment pathway is shown in **Figure 1**. **Figure 1: Proposed positioning of berotralstat in the HAE pathway in the UK**

Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]
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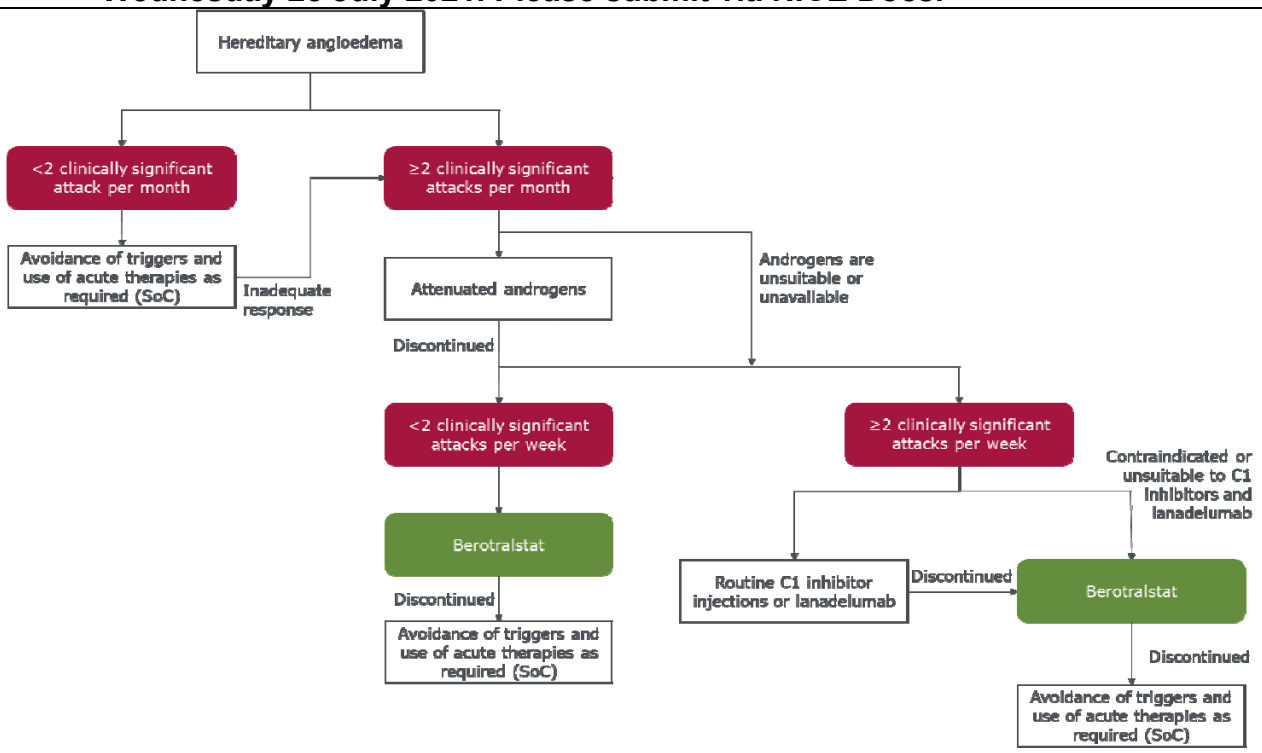

Abbreviations: HAE, hereditary angioedema; SoC, standard of care; UK = United Kingdom

This subgroup of patients was selected by the Company as it was identified by UK clinical experts at a Delphi panel as the population with the highest unmet need in HAE and represents the patients most likely to be treated with berotralstat in UK clinical practice.[1] It is also the population in which berotralstat is most cost-effective in the Company's original base case, and therefore provides the most efficient use of NHS resources.

It should be noted that the revised wording for the positioning has no material impact on the cost-effectiveness analysis, as the revised base case population and associated data remains the same as in the original base case. The company acknowledges, however, that the sample size informing the model is small and has therefore included a scenario analysis in which the model is informed by data from all patients with ≥2 attacks per month (irrespective of androgen use/availability).

The results of the Company revised base case in the two different populations is shown in **in the additional data supplementary appendix file.**

References

1. MAP BioPharma Limited. Hereditary Angioedema (HAE) and potential treatments in the UK: Delphi study Final report. Published online 2020.

2

Issue 2: Clinical evidence suggests berotralstat is more effective than placebo in reducing attack rate, but its effect on attack severity is not known.

<u>In the draft ACD, the appraisal committee stated that:</u>

	"They [patient experts] explained that although the reduction in attack rate is a clinically important outcome for people with hereditary angioedema, the reduction in attack severity would be equally important. They noted that if a treatment did not reduce attack rate, but reduced attack severity, they would still value the option to have that treatment. They further highlighted that the hospitalisation of people with hereditary angioedema is often because of attack severity rather than attack rate…The committee recognised that it is important to consider evidence on attack severity as well as attack rate…[The committee] concluded that the clinical evidence suggests berotralstat is more effective than placebo in reducing attack rate, but its effect on attack severity is not known." **Company response**: The company agrees that attack severity is an important outcome for people with HAE and agrees that a treatment that reduces attack severity and attack rate would be valuable. The original company model base case captures the impact of berotralstat on attack severity using attack location combined with attack duration as objective proxy measures, with data informed by APeX-2 (as outlined below). Additionally, clinicians advised that the need for acute therapy, and the requirement for multiple administrations of acute therapy, also provide measures of attack severity. These proxy measures are objective and rigorous assessments of attack severity. Data from APeX-2 shows that berotralstat reduces attack severity, as measured by attack location. In particular, there was a [redacted] reduction in laryngeal attacks ([redacted]) with berotralstat compared with placebo in APeX-2. Given that laryngeal attacks are potentially life-threatening, berotralstat potentially limits the most severe types of HAE attacks. Similarly, APeX-2 data show that berotralstat reduces attack duration, most notably reducing the mean duration of attack by nearly [redacted] in patients who transitioned from the placebo arm in Part 1 to berotralstat 150mg in Part 2 ([redacted] in placebo Part 1, [redacted] in the same patients transitioning to berotralstat 150mg in Part 2). The impact of berotralstat on attack severity can also be estimated by assessing the number of HAE attacks requiring acute therapy and the rate of acute therapy use per month. In Part 1 of APeX-2, there was a significant [redacted]% reduction in attacks treated with acute therapy in patients treated with berotralstat 150mg compared to placebo ([redacted] vs [redacted] attacks requiring acute therapy per month; [redacted]). In line with this, patients in the berotralstat 150mg arm used [redacted]% fewer doses of acute therapy per month compared to patients in the placebo arm ([redacted] vs [redacted] doses per month; p<[redacted]). Within the economic analysis, the need for actute therapies is captured as part of the cost calculations associated with cost of an attack, and a scenario analysis presented in response to **Issue 9** considers the impact on QoL of including acute therapy administration-related disutilies. Taken together, objective proxies for severity indicate that berotralstat not only reduces HAE attack rate, but also attack severity, compared with placebo.
3	**Issue 3: The company's model structure is acceptable for decision making, but the continuation rule may not be appropriate in clinical practice.**

Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]
Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 28 July 2021. Please submit via NICE Docs.

In the draft ACD, the appraisal committee stated that:

"This [continuation] rule states that people can only continue taking berotralstat if they have a reduction in attack rate of at least 50% compared with baseline by 3 months. However, the committee noted that there was no continuation rule in APEX-2 or the marketing authorisation… The patient experts explained that if people had fewer attacks but did not reach the threshold of a 50% reduction, they would likely want to continue treatment anyway. Also, even if the number of attacks did not decrease, but the severity did, they would consider it beneficial to continue treatment. The committee noted the importance of the patient experts' comments, and was concerned that it would be difficult to implement the continuation rule in clinical practice."

Company response: The Company acknowledges that, although there are limitations with continuation rules, they ensure efficient use of NHS resources by targeting treatment to patients who benefit the most while avoiding unnecessary adverse events in patients not benefitting.

The Company would like to highlight that a continuation rule for berotralstat has already been incorporated into clinical practice. Berotralstat is available under the Early Access to Medicines Scheme (EAMS), and the Blueteq® criteria requires physicians to tick "I confirm that treatment will be stopped if there has not been a clinically significant reduction in the number of significant angioedema attacks (significant attacks are as defined in the NHS England C1-inhibitor for HAE commissioning policy)[3], observed within 3 months of starting treatment".

A continuation rule for berotralstat treatment was deemed appropriate following discussions with UK clinical experts.[1] A Delphi panel of nine UK clinical experts reached a consensus that 3 months after treatment initiation would be a suitable timepoint to assess whether treatment with berotralstat had been successful.[1] Clinicians agreed that a 50% or greater reduction in attack frequency compared to baseline would constitute treatment success.[1]

The Company notes that there are precedents for using continuation rules within HAE. The current C1-INH commissioning policy states that: "If treatment is ineffective after two months (defined as a lack of reduction in attack frequency despite optimised treatment) then treatment with prophylactic C1-inhibitor should be discontinued and alternative therapy options considered".[2] Additionally, NICE has previously recommended technologies with continuation rules designed primarily to maximise efficient use of NHS resources, such as pirfenidone for treating idiopathic pulmonary fibrosis.[3] Based on the above, the Company is confident that a continuation rule for berotralstat can be implemented in clinical practice and provides the most efficient use of NHS resources, and is therefore appropriate for the model base case.

References

1. MAP BioPharma Limited. Hereditary Angioedema (HAE) and potential treatments in the UK: Delphi study Final report. Published online 2020.
2. Specialised Commissioning Team. *Clinical Commissioning Policy: Plasmaderived C1-Esterase Inhibitor for Prophylactic Treatment of Hereditary Angioedema (HAE) Types I and II*. NHS England; 2016:21. https://www.england.nhs.uk/wp-content/uploads/2018/07/Plasma-derived-C1-esterase-inhibitor-for-prophylactic-treatment-of-hereditary-angioesema-types-I-and-II.pdf

3. NICE. 4 Committee discussion | Pirfenidone for treating idiopathic pulmonary fibrosis | Guidance | NICE. NICE. Accessed July 22, 2021. https://www.nice.org.uk/guidance/ta504/chapter/4-Committee-discussion

4

Issue 4: It is appropriate to consider analyses from the subgroup who have used androgens before and the larger subgroup who may have not

In the draft ACD, the appraisal committee stated that:

"Instead, [the company] provided a scenario analysis using clinical evidence from a larger subgroup (n=57) of people with at least 2 attacks per month who may not have previously used androgens. The ERG agreed with using this larger subgroup because it included more patients than the company's proposed positioning subgroup... the committee concluded that it would consider analyses from the subgroup that has had androgens before as well as the larger subgroup who may not have used androgens before"

Company response: The Company acknowledges that there are limitations in the small sample size for the model base case population (patients with ≥2 attacks per month and who have used/are unsuitable for prior androgens) and this may create uncertainties within the cost-effectiveness model.

The Company proposed the positioning of berotralstat as it was identified by clinical experts in a Delphi panel as the population with the highest unmet need in HAE and represents the patients most likely to be treated with berotralstat in UK clinical practice.[1] It is also the population in which berotralstat is most cost-effective and therefore provides the most efficient use of NHS resources. As stated in response to **Issue 1**, the Company has proposed some amends to the berotralstat positioning that have no material impact on the data informing the model base case (see **Issue 1** and **Figure 1**).

To mitigate Committee concerns over the sample size uncertainty, the Company has included a scenario analysis in which the model is informed by data from all patients with ≥2 attacks per month (irrespective of androgen use/availability). The results of the Company revised base case in the two different populations is shown in **the additional data supplementary appendix file** and, crucially, confirms that berotralstat is cost-effective in both populations.

References

1. MAP BioPharma Limited. Hereditary Angioedema (HAE) and potential treatments in the UK: Delphi study Final report. Published online 2020.

5

Issue 5: It is uncertain how much berotralstat reduces attacks compared with standard care beyond the trial follow up period.

In the draft ACD, the appraisal committee stated that:

"…in its revised base case, the company assumed a 0% reduction in attack rate for the standard care arm to be carried forward beyond 6 months in the model. This was different from the ERG's suggested approach to carry forward the average attack rate reduction between months 0 and 6. The ERG explained that the company's approach only removed the placebo effect from the

standard care arm. But it suggested that some placebo effect is also likely in the berotralstat arm as well. The committee suggested it may be more appropriate to adjust the average percentage reduction in attack rate in the berotralstat arm carried forward beyond the observed trial period, using the size of placebo effect seen in the standard care arm."

Company response: The Company accepts that there are limitations in all approaches to the extrapolation of attack rate data for the SOC arm, given that there are only 6 months of data in the placebo arm in APeX-2.

As highlighted during technical engagement, clinical experts at an advisory board stated that they believed that placebo patients in APeX-2 may have experienced a placebo effect, noting that a similar pattern in attack rates for placebo patients was observed in other studies in HAE.[1] Experts stated that the placebo effect may be driven by reduced anxiety and stress and is likely to taper off after several months, once the patient suspects that they are receiving placebo and not active treatment.[1] The high monthly attack rate in the placebo arm at Month 6 of APeX-2 confirms that the placebo effect may have worn off by Month 6.

In contrast, patients in the berotralstat arm experience a consistent and durable decrease in the mean monthly attack rate compared with baseline beyond Month 6. In recently published data from Kiani et al (2021)[2], APeX-2 patients treated with berotralstat 150mg showed a durable reduction from baseline in the HAE attack rate per month across 96 weeks.[2] In fact, the magnitude of benefit with berotralstat increased over time, with mean monthly attack rate generally decreasing steadily from Month 1 through to Month 24. These 24-month data are now included in the model base case and give confidence that the berotralstat treatment effect is not related to a placebo effect. **Please refer to the additional data supplementary appendix file to view the 96-week data.**

In contrast, clinical experts at an advisory board expected the placebo effect with placebo to taper off after several months.[1] APeX-2 was a double-blinded trial in which patients may have believed that they were randomised to receive berotralstat when in actuality were treated with placebo. Given the role of stress and anxiety in driving attack rates in HAE, patient belief of being on active treatment may have led to a reduction in their stress and anxiety, which is reflected in the short-term reduction in attack rate in the placebo arm of APeX-2. Furthermore, as noted by clinical experts at an advisory board,[1] patients typically experience an improved level of overall care in a clinical trial than in clinical practice, which may have influenced the reduction in attack rate for placebo patients despite the lack of active prophylactic therapy. Based on the above, it is implausible to expect that HAE attacks would be reduced over a 96-week period in the placebo arm of APeX-2.

Based on the above, and acknowledging the Committee concerns regarding the SOC extrapolations, the Company has revised the model base case extrapolations to a more conservative approach than in the original model base case. In the revised Company base case, rather than using the pooled baseline attack rate for the SOC extrapolations, the placebo attack rate is gradually tapered from months 6-12 to reflect the clinical expert opinion that the placebo effect would taper off after several months.[1] The revised model approach to extrapolating the berotralstat and SOC arms is as follows:

	• **Berotralstat:** uses the observed APeX-2 study data for berotralstat 150mg up to the last observation (Month 24), after which the mean monthly attack rate from month 4 to 24 is applied over the remainder of the model time horizon. • **SOC:** uses the observed APeX-2 study data for placebo up to the last observation (Month 6). At Month 7, the mean monthly attack rate over months 1-6 is applied and is then tapered to the pooled baseline attack rate in a linear fashion in months 7-12. From Month 12 onwards, the pooled baseline attack rate is applied for the SOC arm. The Company is confident that the inclusion of 96-week data for berotralstat 150mg, and tapering of the placebo effect for SOC, represents the most realistic and clinically plausible approach to extrapolating the beyond the APeX-2 trial follow-up period and is a more conservative approach than the original base case. **Please refer to the additional data supplementary appendix file to view the revised base case model results.** **References** 1. *UK Advisory Board. BioCryst Data on File. 29 March 2021*. 2. Kiani S. Durable Reduction in Hereditary Angioedema (HAE) Attack Rates with Berotralstat Over 24 Months: Results from the Phase 3 APeX-2 Study. Presentation presented at the: EAACI Digital Congress; 2021; Virtual.
6	**Issue 6: Additional analysis using utility values that reflect attack severity as well as attack rate reduction would be preferable.** <u>In the draft ACD, the appraisal committee stated that:</u> *"The committee was concerned that using utility values directly from APEX-2 may not adequately capture the effect of attacks on health-related quality of life and do not reflect the effect of attack severity. But it noted that the latter was likely to apply to the utility values from Nordenfelt et al. too. The committee concluded that additional analysis using utility values that reflect attack severity as well as attack rate reduction would be preferable."* **Company response:** The company agrees that attack severity is an important outcome for people with HAE and agrees that a treatment that reduces attack severity and attack rate would be valuable. As outlined in response to **Issue 2**, the original Company model base case captures the impact of berotralstat on attack severity using attack location combined with attack duration as proxies and showed that berotralstat reduces attack severity compared with placebo. Berotralstat also reduces the need for acute therapies to manage attacks, further confirming its impact on severity, and this is captured in the model cost calculations. These proxy measures are an objective and rigorous assessment of attack severity in the absence of other objective measures from APeX-2. In the model, a single disutility value (based on data from Nordenfelt et al. 2014)[1] is applied for the duration of each HAE attack. Given that attack duration is used as a proxy for severity, the utility values in part reflect both attack severity as well as attack rate. The Company considers this to be a conservative approach and may not fully capture the value of berotralstat in reducing attack severity compared with placebo.

	In an attempt to factor in the quality of life implications of berotralstat reducing the need for acute therapies compared to standard of care (a proxy for attack severity), a scenario is considered in which an administration disutility is applied when a patient requires injectable acute therapy. Further details are presented in the response to **Issue 9**. **References** 1. Nordenfelt P, Dawson S, Wahlgren C-F, Lindfors A, Mallbris L, Björkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. Allergy Asthma Proc. 2014;35(2):185-190. doi:10.2500/aap.2014.35.3738
7	**Issue 7: It is not appropriate to include health-related quality of life effects for carers in the base case.** <u>In the draft ACD, the appraisal committee stated that:</u> *"…the committee noted that although many diseases and conditions may adversely affect carers, few technology appraisals model this. For example, carer disutility was not included in a previous appraisal in this disease area (see NICE technology appraisal guidance on lanadelumab)…the committee concluded that it was not appropriate to include health-related quality of life effects for carers in the base case."* **Company response:** The Company acknowledges that other HAE appraisals do not apply a caregiver disutility. However, it is within the remit of NICE to consider caregiver burden, with the reference case stating that the following should be considered: "all direct health effects, whether for patients or, when relevant, carers". Caregivers of patients with HAE experience considerable burden from time spent offering both physical and emotional support, as well as shared anxiety over attacks.[2,3] HAE attacks can be fatal and many are very disabling, with patients confined to bed for hours or days, or left without use of their limbs.[4] Due to the hereditary nature of the disease, many carers may also be HAE patients, who not only fear for their own attacks, but also the attacks of those to whom they are providing care. HAE attacks can end in death[4] and patients with HAE may have relatives who have died from an attack. This fear of death was highlighted by clinical experts at an advisory board, who agreed it was common and a key component of attack-related anxiety.[1] In the Company economic analysis, the caregiver disutility of [redacted], while substantial, is only applied when patients are experiencing an attack. Additionally, caregiver disutility is only applied to 52.4% of attacks to align with the proportion of patients who reported receiving assistance from a caregiver during their last attack in Aygören-Pürsün *et al.* (2014).[2] Taken together, therefore, the caregiver disutility is only applied for an average of [redacted] days per monthly cycle for berotralstat ([redacted]% of time per month) and [redacted] days per monthly cycle for SOC ([redacted]% of time per month). Given the anxiety and stress among both patients with HAE and their caregivers, the Company is

	confident that these assumptions are conservative. For example, an alternative approach could be to assume that all attacks requiring acute therapy need caregiver support. Using this assumption, a caregiver disutility would be applied to [redacted]% of attacks with SOC and [redacted]% of attacks with berotralstat. This would mean that caregiver disutility would have a much greater influence on the analysis when compared with the 52.4%[2] of attacks used in the base case model. Despite the clear and documented caregiver burden of HAE, the Company accepts that previous HAE appraisals did not consider caregiver burden and has amended the base case analysis to remove carer disutility. The Company has included a scenario analysis in which carer disutility is included in the economic model. In both scenarios, berotralst is dominant versus standard of care. **References** 1. *UK Advisory Board. BioCryst Data on File. 29 March 2021*. 2. Aygören-Pürsün E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. *Orphanet J Rare Dis*. 2014;9:99. doi:10.1186/1750-1172-9-99 3. HAE international, Copenhagen Economics. HEREDITARY ANGIOEDEMA IN THE UK, Survey and model results. Published online October 2020. 4. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol*. 2012;130(3):692-697. doi:10.1016/j.jaci.2012.05.055
8	**Issue 8: The cost-effectiveness estimates are highly uncertain, and some are substantially higher than £20,000 per QALY gained.** <u>In the draft ACD, the appraisal committee stated that:</u> *"The cost-effectiveness estimates were substantially uncertain because of: uncertainty about the attack rate reduction beyond the trial follow-up…the small patient numbers from APeX-2…the acceptability of the treatment continuation rule in clinical practice…attack severity not reflected in the utility estimate. For some clinically plausible scenarios the ICERs were substantially higher than £20,000 per quality-adjusted life year (QALY) gained. So berotralstat cannot be recommended."* **Company response**: The Company acknowledges the issues raised by the Committee and has therefore provided a revised base case in **the additional data supplementary appendix** to reduce uncertainty. The revised base case demonstrates that berotralstat is dominant compared with SOC in both the ≥2 attacks population and the prior androgen population. In developing the revised base case ICER, the Company has acknowledged and/or directly addressed all of the key concerns raised by the committee regarding the ICER uncertainty: • **Uncertainty about attack rate extrapolation:** See response to Issue 5. • **Small patient numbers in APeX-2:** See response to Issues 1 and Issue 4.

	• **Acceptability of continuation rule in clinical practice:** See response to Issue 3. • **Inclusion of attack severity:** See response to Issue 2 and Issue 6. The Company has also attempted to reduce some of the long-term uncertainty by including 96-week data from APeX-2 for patients treated with berotralstat 150mg. In addition to this, the Company has access to preliminary data on patients using berotralstat in real-world clinical practice in the UK, as part of the Early Access to Medicines Scheme (EAMS). A summary of key findings from the EAMS data is shown in the **additional data supplementary appendix file**.
9	**Issue 9: Berotralstat is an innovative prophylactic treatment for recurrent attacks of hereditary angioedema.** In the draft ACD, the appraisal committee stated that: *"The committee considered berotralstat to be innovative because it would be the first licensed oral prophylactic treatment option for people with recurrent attacks of hereditary angioedema. This would mean people would have access to medicine that is more convenient than injectables…The committee concluded that berotralstat is an innovative prophylactic treatment for recurrent attacks of hereditary angioedema, but all relevant benefits are reflected in the cost-effectiveness estimates."* **Company response**: The Company was pleased to note that the Committee acknowledged the high unmet need in HAE and that the committee considers berotralstat to be innovative and urges the Committee to take these considerations into account in their decision-making. The Company agrees with the Committee that HAE can be a severe and debilitating condition and that there is a lack of effective prophylactic options. The urgent need for effective prophylactic therapies should be taken into consideration when evaluating the cost-effectiveness of berotralstat. The Company also agrees with the Committee that berotralstat is innovative and offers the first and only licenced oral prophylactic treatment option for people with recurrent attacks of HAE. As described in the response to **Issue 2**, APeX-2 trial data show that berotralstat reduces the need for acute therapy compared with placebo. Given that acute therapies are administered via subcutaneous or intravenous injections, the Company considers the oral mode of administration to be an important additional benefit of berotralstat. In fact, a report from Holko et al (2018)[1] demonstrates that oral therapies are associated with a utility benefit of 0.164 and 0.147 over intravenous or subcutaneous therapies, respectively, in patients with inflammatory bowel disease.[1] Similarly, a study on treatment satisfaction in HAE patients found that 50% of patients prefer non-invasive methods of administration, while another study reported that 62% of respondents who used a peripheral vein to administer treatment reported difficulty finding a vein or getting the infusion to work properly.[2,3] Fear of needles, injection site reactions, hard-to-find veins, and the increased burden on the NHS for treatment administration, are all problems that could be addressed by the reduced HAE attack rate and need for acute therapy in patients who use berotralstat versus SOC.

Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]
Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 28 July 2021. Please submit via NICE Docs.

	While the revised model base case conservatively excludes any potential benefits of berotralstat's mode of administration, the Company has provided a scenario in which administration disutilites are applied for attacks requiring acute therapy and depending on the acute therapy received, using data from Holko et al (2018).[1] **Please refer to the additional data supplementary appendix file to view the revised base case and scenario model results** and shows that berotralstat is dominant in both scenarios. **References** 1. Holko P, Kawalec P, Mossakowska M. Quality of life related to oral, subcutaneous, and intravenous biologic treatment of inflammatory bowel disease: a time trade-off study. Eur J Gastroenterol Hepatol. 2018;30(2):174-180. doi:10.1097/MEG.0000000000001031 2. Riedl MA, Banerji A, Busse PJ, et al. Patient satisfaction and experience with intravenously administered C1-inhibitor concentrates in the United States. Annals of Allergy, Asthma & Immunology. 2017;119(1):59-64. doi:10.1016/j.anai.2017.05.017 3. Jose J, Lehman EB, Craig T. Evaluating satisfaction of patients with hereditary angioedema with their past and present treatments: Implications for future therapies. Allergy and Asthma Proceedings. 2018;39(1):74-80. doi:10.2500/aap.2018.39.4095

Insert extra rows as needed

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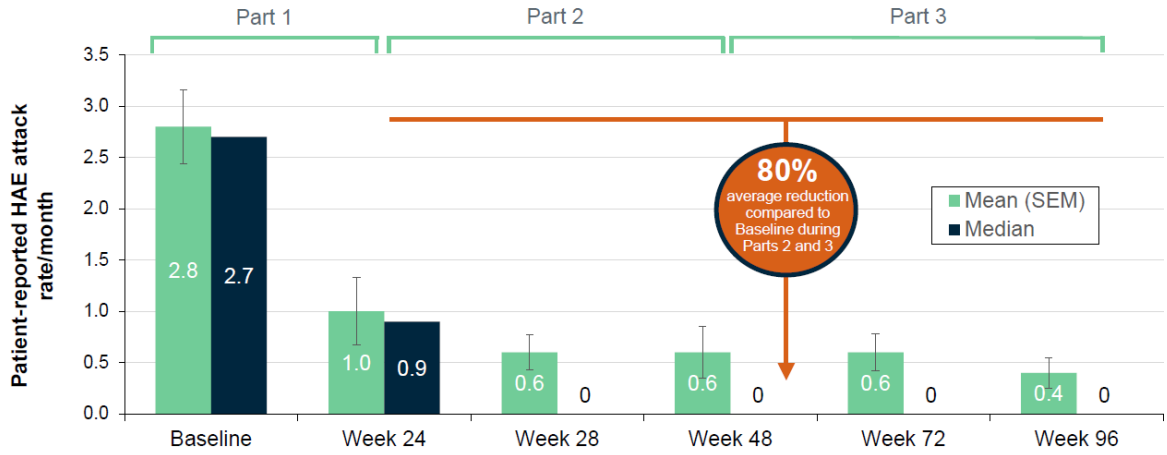
ID1624: Additional data supplementary appendix

Appendix 1: New clinical data supporting berotralstat

Long-term data from APeX-2

In recently published data from Kiani et al (2021)[5], APeX-2 patients treated with berotralstat 150mg showed a durable reduction from baseline in the HAE attack rate per month across 96 weeks (Figure 2).[1] In fact, the magnitude of benefit with berotralstat increased over time, with mean monthly attack rate generally decreasing steadily from Month 1 through to Month 24. These 24-month data are now included in the model base case and give confidence that the berotralstat treatment effect is not related to a placebo effect.

Figure 1: HAE attack rate per month with berotralstat 150mg in APeX-2



Abbreviations: HAE, hereditary angioedema; SEM, standard error of the mean
Source: Kiani et al. EAACI 2021 (Abstract 170)[1]

Data from the Early Access to Medicines Scheme for berotralstat

The Company has also attempted to reduce some of the long-term uncertainty by including 96-week data from APeX-2 for patients treated with berotralstat 150mg. In addition to this, the Company has access to preliminary data on patients using berotralstat in real-world clinical practice in the UK, as part of the Early Access to Medicines Scheme (EAMS). A summary of key findings from the EAMS data is shown below and provides confidence of berotralstat's real-world effectiveness:

- [redacted] At the point of the data cut, [redacted] patients have received berotralstat as part of the EAMS program. This highlights the unmet need and demand for an effective prophylactic treatment for HAE in UK practice.
- [redacted] Among the [redacted] patients with at least one order of berotralstat, the average baseline attack rate was [redacted] attacks per month in the three months prior to initiating berotralstat. By contrast, the pooled baseline attack rate in APeX-2 was [redacted].
- [redacted]: For the [redacted] patients who have been part of the EAMS process for long enough to have two orders of berotralstat at the point of the EAMS data cut, the pack-adjusted monthly attack rate reduced by [redacted]%, from [redacted] attacks per month in the three months prior to initiating berotralstat, to [redacted] attacks per month at the point of the second

EAMS order of berotralstat. The reduction was even greater in the [redacted] patients who had been part of the EAMS for long enough to have four orders of berotralstat, who experienced an [redacted]% reduction in monthly attack rate ([redacted] at baseline vs [redacted] at order 4).

- [redacted]**:** Within the EAMS data, information is also available on the use of actute therapies during each order period. The data suggests that patients use notably less acute therapy as time progresses. At the time of the first order, the percentage of patients who received Berinert, Ruconest, Cinryze, Firazyr are [redacted]%, [redacted]%, [redacted]%, and [redacted]% respectively. This reduced to [redacted]%, [redacted]%, [redacted]% and [redacted]% at the time of order 2, [redacted]%, [redacted]%, [redacted]%, and [redacted]% at the time of order 3, and [redacted]%, [redacted]%, [redacted]%, and [redacted]% at the time of order 4. This demonstrates a consistent [redacted] This aligns with the findings from APeX-2, where patients receiving berotralstat required less use of acute therapy than patients on SoC due to better disease control.

Appendix 2: New model base case

Summary of the revised model base case

A summary of the key parameters in the revised model base case is provided in **Table 1**.

Table 1: Revised company base case: key parameters

Parameter	Revised company base case
Population	≥2 attacks per month and prior androgen use/unsuitable/unavailability
Continuation rule	Yes
Caregiver disutility	No
Administration disutility	No
Berotralstat attack rate extrapolation	Observed APeX-2 berotralstat data from Month 0-24. Mean attack rate from Month 4-24 extrapolated over remainder of time horizon.
Standard of care attack rate extrapolation	Observed APeX-2 placebo data from months 0-6. From months 7-12, mean placebo attack rate tapered to baseline. From Month 12, pooled baseline attack rate extrapolated over the remainder of the time horizon.
Berotralstat price per year	£[redacted]

Summary of changes to the model base case

A number of changes have been applied to the berotralstat economic model in response to the ACD. These changes were made to align with committee recommendations and reduce the uncertainty around model inputs. **Table 2** provides a summary of the changes to the economic analysis following the most recent response to the ERG and ACD. Further details of each update are presented in the following subsections.

Table 2. Amendments to model base case

Modelling alteration	Previous assumption/data	Updated assumption/data
Inclusion of long-term berotralstat attack rate data from APeX-2	Used APeX-2 data up to week 48 of the study	Uses APeX-2 data up to week 96 of the study
Extrapolation of SoC attack rate	Patients on SoC were assumed to revert to baseline attack rate for the remainder of the time horizon	Patients on SoC attack rate tapers to baseline over time
Carer disutility	Caregiver disutility is applied for the time spent in attacks, for a percentage of attacks	No caregiver disutility is applied
Average attack rate calculations	The mean attack rate for both berotralstat and SoC patients is weighted by the number of observations at each time point	The mean attack rate for both berotralstat and SoC patients is **not** weighted by the number of observations at each time point
Updated berotralstat price	Berotralstat price per year was £[redacted]	Berotralstat price per year is updated to £[redacted]

Abbreviations: SoC, Standard of Care

Inclusion of long-term berotralstat attack rate data from APeX-2

Since the date of the original submission, long-term follow-up data from APeX-2 have become available and are able to inform the attack rate for patients receiving berotralstat for up to 96 weeks. The inclusion of long-term attack rate data for patients receiving berotralstat helps to provide confidence in its long-term effectiveness.

The mean attack rates for berotralstat from Month 12 (48 weeks) to Month 24 (96 weeks) in each population is presented in **Table 3**. **Figure 2** presents a graph of the mean attacks rates per month

from baseline to month 24. The data clearly show a consistent and durable reduction in monthly attack rate over 96 week with berotralstat, with attack rate reduction continuing to decrease over time.

In the updated model, these additional attack rate data were included for the base case population (≥2 attacks per month at baseline with prior androgen use/unavailability), the ≥2 attacks per month at baseline population, and in berotralstat responsers in each population. In the revised model base case, the berotralstat attack rate reduction from Months 1 to 24 is informed by the observed APeX-2 trial data. After Month 24, the mean monthly attack rate is from Months 4 to 24 is applied for the remainder of the time horizon. **Table 4** presents the mean monthly attack rate reduction from baseline from Month 4 to 24 in all of the key populations in the model.

The impact of the adding the 96-week data is to increase the confidence in the berotralstat long-term effectiveness and therefore improve the berotralstat ICER.

Table 3: Long term reduction in mean attack rate for patients receiving berotralstat

Percentage reduction in attack rate	Month												Source
	13	14	15	16	17	18	19	20	21	22	23	24	
Base case population	[redacted]												APeX-2
≥2 attacks at baseline population	[redacted]												APeX-2
Base case population (responders)	[redacted]												APeX-2
≥2 attacks at baseline population (responders)	[redacted]												APeX-2

Base case population: ≥2 attacks per month at baseline and prior androgen use/unsuitability

Table 4: Average reduction in attack rate from months 4 to 24

Percentage reduction in attack rate	Average percentage reduction in attack rate from months 4 to 24	Source
Base case population	[redacted]	APeX-2
≥2 attacks at baseline population	[redacted]	APeX-2
Base case population (responders)	[redacted]	APeX-2
≥2 attacks at baseline population (responders)	[redacted]	APeX-2

Base case population: ≥2 attacks per month at baseline and prior androgen use/unsuitability

Figure 2: Attack rate from baseline to month 24

Trend line indicates that the mean monthly attack rate continues to decline with longer use of berotralstat, demonstrating its long-term effectiveness

Extrapolation of standard of care attack rate

Over the observed 6 months of follow-up for placebo patients in APeX-2, there was consistently a reduction in attack rate from baseline. From a clinical perspective, the only justifiable explanation for this would be that placebo patients were experiencing a placebo effect, especially considering that anxiety and stress that can contribute to variation in a patients attack rate.[2]

While the revised model base case approach has been modified to factor a longer term placebo effect into the analysis, we believe that the previous approach (using the pooled baseline attack rate over the entire time horizon) offers a more realistic simulation of attack rates over time for patients receiving SOC.

In the Company revised base case analysis, a more conservative approach has been implemented in which it is assumed that the placebo effect benefit will taper to baseline over time, in line with comments during a clinical advisory board.[2] The clinical rationale for a tapering of the placebo effect is that patients lose belief that they are receiving active therapy after noticing no significant improvement in attack rate.

In the updated base case analysis, the observed APeX-2 trial data from the placebo arm is used from baseline to Month 6. At Month 7, the mean monthly attack rate over months 1-6 is applied and is then tapered to the baseline attack rate in a linear fashion from months 7-12. From Month 12 onwards, the pooled baseline attack rate is applied for the SOC arm. A graphical representation of the SOC attack rate based on revised model base case assumptions is presented in **Figure 3**. Month 12 was conservatively selected as the point at which the placebo effect would no longer occur based on clinical expert comments at an advisory board.[2]

Figure 3: Revised model base case SOC and bertoralstat attack rates extrapolations

SOC: *APeX-2 placebo attack rate data are used from months 1-6. From months 7-12 the mean attack rate from months 1-6 is tapered to baseline. After Month 12, the pooled APeX-2 baseline attack rate is applied.*
Berotralstat: *APeX-2 berotralstat attack rate data are used up to Month 24, after which the mean rate in months 4-24 is applied.*
Abbreviations: SoC, standard of care

Carer disutility

The original Company analysis applied a caregiver disutility for the for the mean attack duration to 52.4% of attacks, based on the percentage of attacks that required assistance from a caregiver presented in Aygören-Pürsün et al., 2014.[3] Based on Committee recommendations, the updated base case analysis no longer applies any caregiver disutility. A scenario has been included in which carer disutility is applied (see table 8 below).

Average attack rate calculations

In the previous analysis, the mean attack rate over the observed follow-up in APeX-2 is weighted based on the number of patients who provided data at each time point. Due to some patients discontinuing treatment over time and the addition of the berotralstat 96-week data, this approach gives greater weighting to the attack rates observed in the earliest months, where patient numbers are highest. As can be seen from **Figure 2**, the attack rate for berotralstat patients consistently declines over time. This makes giving the highest weighting to the earliest observations counterintuitive, as they are the least representative of the long-term clinical response.

Therefore, the updated analysis does not weight the average attack rate calculations based on patient numbers.

Berotralstat price

We have submitted a revised model base case and various scenario analyses that acknowledge and/or implement the Committee recommendations and reduce uncertainty in the berotralstat incremental cost-effectiveness ratio (ICER). To further reduce uncertainty, we have also extended the confidential simple patient access scheme (PAS) discount such that the fixed discounted price for a pack of 28 capsules is reduced from £[redacted] in the previous model to £[redacted] in the revised Company base case. This simple PAS represents a [redacted]% discount on the list price of

berotralstat and means the cost per patient per year is reduced from £[redacted] to £[redacted]. This emphasises our commitment to ensuring patients in the UK have much-needed access to berotralstat.

Revised base case model results: cost-effectiveness

The revised base case model shows that berotralstat is dominant compared with standard of care.

Table 5: Revised model base case cost-effectiveness results

	Berotralstat	SoC
Revised Company base case		
Total LYG	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Incremental LYG		[redacted]
Incremental QALYs		[redacted]
Incremental costs (£)		[redacted]
ICER versus SoC (£/QALY)		Berotralstat dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care

Revised base case model results: Sensitivity analyses

One way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA) were conducted for the revised base case assumptions to identify which parameters have the greatest influence on the results and to demonstrated how robust the model is to variation across all parameters.

Due to the base case analysis generating an ICER in which berotralstat is dominant, the OWSA investigated the impact on the net monetary benefit (NMB) for SoC when compared against berotralstat. The impact on the NMB for the top 15 most influential parameters, when varied to an upper and lower limit, are presented in a tornado diagram in **Figure 4**. It can be seen that the most influential parameter is the pooled baseline attack rate, followed by the proportion of SoC attacks that require acute therapy and then the price of berotralstat.

Figure 4: OWSA tornado diagram

Abbreviations: NMB, net monetary benefit; OWSA, one-way sensitivity analysis; SOC, standard of care

The PSA was run over 10,000 iterations and the mean results are presented in **Table 6**. The incremental cost-effectiveness plane (ICEP) and cost effectiveness acceptability curve (CEAC) are presented in **Figure 5** and **Figure 6** respectively.

The mean results of the PSA are very similar to those of the base case analysis, which demonstrates that the analysis is robust to variations in the model parameters. The ICEP shows that berotralstat generates more QALYs than SoC for every iteration of the PSA, which demonstrates that berotralstat is undoubtedly the most clinically effective treatment. Most of the , showing that berotralstat is also . The 95% confidence interval shows the incremental costs to be between £ and £. The CEAC shows that there is an 86.4% probability of berotralstat being cost effective at a willingness to pay threshold of £20,000 and an 86.9% chance of being cost effective at a willingness to pay threshold of £30,000. Taken together, the sensitivity analyses provide confidence that berotralstat is a cost-effective option for HAE in the UK.

Table 6: Mean PSA results

	Berotralstat	SoC
Revised Company base case		
Total LYG		
Total QALYs		
Total costs (£)		
Incremental LYG		
Incremental QALYs		
Incremental costs (£)		
ICER versus SoC (£/QALY)		Berotralstat dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care

Figure 5: Incremental cost-effectiveness place

Abbreviations: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 6: Cost-effectiveness acceptability curve

Revised model base case results: Model population scenario analysis

The results of the Company revised base case in the two different populations (≥2 attacks/month with prior androgen use and ≥2 attacks/month irrespective of androgen use) is shown in **Table 7** and shows that berotralstat is dominant in both populations, mitigating concerns from the Committee around the uncertainty in the model.

Table 7: Scenario analysis: investigating the impact of adjusting the model population

	Berotralstat	SoC
Revised Company base case		
Total LYG	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Incremental LYG		[redacted]
Incremental QALYs		[redacted]
Incremental costs (£)		[redacted]
ICER versus SoC (£/QALY)		Berotralstat dominant
Revised Company base case in ≥2 attacks population (irrespective of androgen use/availability)*		
Total LYG	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Incremental LYG		[redacted]
Incremental QALYs		[redacted]
Incremental costs (£)		[redacted]
ICER versus SoC (£/QALY)		Berotralstat dominant

**All parameters in line with revised Company base case except that the data informing the model are the APeX-2 population with ≥2 attacks per month at baseline (irrespective of androgen use/availability).*
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care

Revised model base case results: Caregiver disutility scenario analysis

The Company has included a scenario analysis in which carer disutility is included in the economic model. In both scenarios, berotralst is dominant versus standard of care.

Table 8: Scenario analysis: Investigating the impact of including caregiver disutility

	Berotralstat	SoC
Revised Company base case		
Total LYG	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Incremental LYG		[redacted]
Incremental QALYs		[redacted]
Incremental costs (£)		[redacted]
ICER versus SoC (£/QALY)		Berotralstat dominant
Revised Company base case with caregiver disutility included*		
Total LYG	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Incremental LYG		[redacted]
Incremental QALYs		[redacted]
Incremental costs (£)		[redacted]
ICER versus SoC (£/QALY)		Berotralstat dominant

**All parameters in line with revised Company base case except that a caregiver disutility is applied for the duration of each attack for 52.4% of attacks..Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care*

Revised model base case results: Administration disutility scenario analysis

While the revised model base case conservatively excludes any potential benefits of berotralstat's mode of administration, the Company has provided a scenario in which administration disutilites are applied for attacks requiring acute therapy and depending on the acute therapy received, using data from Holko et al (2018).[4] The scenario is provided in **Table 9** and shows that berotralstat is dominant in both scenarios.

Table 9: Scenario analysis: Investigating the impact of including administration disutility

	Berotralstat	SoC
Revised Company base case		
Total LYG	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Incremental LYG		[redacted]
Incremental QALYs		[redacted]
Incremental costs (£)		[redacted]
ICER versus SoC (£/QALY)		Berotralstat dominant
Revised Company base case with administration disutility included*		
Total LYG	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Incremental LYG		[redacted]
Incremental QALYs		[redacted]
Incremental costs (£)		[redacted]
ICER versus SoC (£/QALY)		Berotralstat dominant

**All parameters in line with revised Company base case except that an administration disutility is applied for the number of days per month a patient has an attack requiring acute therapy, using utility values from Holko et al (2018).*[4]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; SoC, standard of care

Complete list of economic modelling updates

Table 10 presents a complete list of all changes that have been applied to the economic model that have contributed to a change in the results, along with their location within the model.

Table 10. Amendments to model base case

Model parameter updated	Updated value	Location in the economic model
Berotralstat: reduction of attack rate from baseline, month 13	[redacted]	Clinical inputs H73
Berotralstat: reduction of attack rate from baseline, month 14		Clinical inputs H74
Berotralstat: reduction of attack rate from baseline, month 15		Clinical inputs H75
Berotralstat: reduction of attack rate from baseline, month 16		Clinical inputs H76
Berotralstat: reduction of attack rate from baseline, month 17		Clinical inputs H77
Berotralstat: reduction of attack rate from baseline, month 18		Clinical inputs H78
Berotralstat: reduction of attack rate from baseline, month 19		Clinical inputs H79
Berotralstat: reduction of attack rate from baseline, month 20		Clinical inputs H80
Berotralstat: reduction of attack rate from baseline, month 21		Clinical inputs H81
Berotralstat: reduction of attack rate from baseline, month 22		Clinical inputs H82
Berotralstat: reduction of attack rate from baseline, month 23		Clinical inputs H83
Berotralstat: reduction of attack rate from baseline, month 24		Clinical inputs H84
Berotralstat: average reduction of attack rate from baseline, from month 24		Clinical inputs H86
SoC: reduction of attack rate from baseline, month 7 (estimated)	[redacted]	Clinical inputs H95
SoC: reduction of attack rate from baseline, month 8 (estimated)		Clinical inputs H96
SoC: reduction of attack rate from baseline, month 9 (estimated)		Clinical inputs H97
SoC: reduction of attack rate from baseline, month 10 (estimated)		Clinical inputs H98
SoC: reduction of attack rate from baseline, month 11 (estimated)		Clinical inputs H99
SoC: reduction of attack rate from baseline, month 12 (estimated)		Clinical inputs H100
SoC: average reduction of attack rate from baseline, from month 6		Clinical inputs H102
Caregiver burden: additional disutilities	No	Executive summary E24:F24

Abbreviations: SoC, standard of care

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4. Holko P, Kawalec P, Mossakowska M. Quality of life related to oral, subcutaneous, and intravenous biologic treatment of inflammatory bowel disease: a time trade-off study. *Eur J Gastroenterol Hepatol*. 2018;30(2):174-180. doi:10.1097/MEG.0000000000001031

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	HAE UK (Patient support and advocacy charity for people and families affected by Hereditary Angioedema)
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	HAE UK is very concerned that the only currently licensed form of prophylaxis that is an oral formulation rather than an injectable will not be available to patients in the UK. Oral presentation is of great benefit to patients who have poor venous access or are not otherwise able to inject, or who may be in a situation where injecting is impractical
2	Attacks of HAE (if left untreated) are of long duration, sometimes 2 to 3 days before complete resolution, leaving patients exhausted and debilitated. This is not always fully appreciated. Some patients are managed by a carer (usually a family member) who administers injections and carries out other tasks whilst the patient is undergoing an attack. The condition therefore affects the life and livelihood of more than one person.
3	The current positioning is of advantage to allow prophylaxis to patients who do not currently qualify for injectable prophylactic treatment (C1-INH or lanadelumab) and yet still have recourse to frequent and extensive use of C1-INH or icatibant in order to manage attacks of Hereditary Angioedema (HAE). Prophylaxis for these patients will reduce the burden of the condition to patients, the NHS and carers.
4	HAE UK supports the discontinuation of the use of berotralstat if there is inadequate response.
5	As with all forms of prophylaxis it would not be reasonable to expect this to be a life-long treatment, but may be very appropriate used, for example, to see a young person through school exam periods and university/college. Otherwise, attacks of HAE may affect their exam performance, course work and ultimate life chances.
6	

Insert extra rows as needed

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- 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):	British Society of Allergy and Clinical Immunology
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
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1	Stopping therapy if ineffective is raised as possibly not clinically appropriate in practice; it is unlikely the technology would be continued if not effective; it would be reasonable to consider normal practice to review stable patients every 6 months, and those requiring a new therapy / intervention earlier than this. When commencing prophylaxis patients will generally be reviewed every 6-12 weeks. If prophylaxis if not effective at the recommended dose then it is likely that the treatment would be stopped at that stage. This would be normal practice when considering prophylaxis with attenuated androgens, they would be stopped if not effective. Overall a 50% reduction in disease would be a reasonable assumption for effectiveness and would support ongoing use in those with the greatest benefit
2	It is important to highlight that HAE as a condition can be significantly impacted by psychological state. Although the disease will often be stable when averaged over life, fluctuations are common related to life factors. Flares / increase in activity can often be seen at times of marked stress, and improvement when there is less stress / enhanced confidence. This could exacerbate the placebo effect of being in a clinical trial when compared to other diseases – and this might impact on the modelling of the placebo effect in the control arm. This could explain the initial reduction in disease activity following enrolment and then the return / overshoot of baseline attack rate seen in the placebo group
3	The selection of the proposed treatment group being those with 2 or more attacks is reasonably based as these are likely to be the patients with moderate to severe disease and most likely to benefit. Patients with attacks less frequently are generally less inclined to take regular or preventative therapy to avoid attacks. Certainly, when considering attenuated androgen prophylaxis most patients with less frequent attacks will not commence prophylaxis. Although it would be an advantage to be able to offer all patients all treatment options it is already a reality in this condition that there are criteria for access and being able to offer this technology to patients that currently do not have a suitable other option would be a real advantage. In other intermittent conditions for example spontaneous urticaria and angioedema, often patients will only take a prophylactic therapy if events are more frequent than 1-2 times monthly
4	Although severity assessment and inclusion in treatment decisions may be an advantage in HAE there are currently no suitable and easy to use severity tools that are in widespread clinical use. Perhaps it is aspirational to include this aspect – arguably ideal, but maybe not practical currently in routine clinical practice
5	
6	

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[UKPIN]
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1	If there was a continuation rule, this would likely be implemented in clinical practice. There is precedent for continuation rules already in the C1 inhibitor prophylaxis commissioning policy for HAE, as well as in the use of omalizumab for treatment of chronic spontaneous urticaria (which is a different condition, but also has angioedema as one its clinical features).
2	In section 3.5, it is stated that effect on attack severity is not known – however, surrogate measures like attack duration and amount of rescue medication usage can be used as measures of severity – it would be useful to know if these were looked at when considering the effect of berotralstat on attack severity.
3	
4	
5	
6	

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- Do not use abbreviations
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NICE National Institute for Health and Care Excellence

Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

Consultation on the appraisal consultation document – **deadline for comments 5pm on Wednesday 28 July 2021.** Please submit via NICE Docs.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Takeda UK Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No links to the tobacco industry**
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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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 welcome increased treatment options for hereditary angioedema patients and clinicians. We believe that the primary aim of treatment should be attack freedom when achievable and aligned to individual patients' needs and wishes. We agree with the Committee's view that a reduction in the severity of the attacks is important, however note that all attacks can affect daily life for patients living with hereditary angioedema. A German study by Bork *et al*. (Mayo Clin Proc. 2000 Apr;75(4):349-54) highlighted the risks associated with laryngeal oedema attacks in patients with hereditary angioedema. The study included a retrospective survey of 58 patients, of which 23 died due to asphyxiation (40%). This study highlights that laryngeal oedema attacks may be fatal in patients with frequent attacks as well as those with rare episodes of swelling. In addition, as acknowledged by the company, the measurement of attack severity can be subjective. Therefore, whilst severity of attacks is important to consider, the primary goal of treatment should be to reduce the total number of attacks so that patients can, wherever possible, maintain an attack-free life. We believe that informed patient choice and clinical opinion should dictate treatment decisions.
2	
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	HAE UK (support charity for people with hereditary angioedema)
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:	**Rachel Annals**

Comment number	**Comments** Insert each comment in a new row.

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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	My attacks would be very long (3 or so days) if untreated. This would mean I couldn't work or manage day-to-day activities and I would need to reply on support from family or friends for care of my daughter. This shows that it is not just the patient who is affected, but it has a direct impact on my daughter's wellbeing and my need for support from others. I think this is an important point to consider.
2	I firmly believe patients should have a choice as to which medication they choose to take. There is currently no licensed oral prophylactic medication for patients, meaning those with poor vein access or those with a fear of needles, are limited in their choices and would rely more on carers or hospital staff to help with administration. Stress is a big trigger for many peoples attacks and having no prophylactic medication can cause unnecessary anxiety and stress about an attack occurring.
3	I would support the discontinuation of Berotralstat if I didn't receive a good response from treatment. I feel a 3 month trial period is sufficient to know whether it would work for me.
4	Currently many patients do not fit the criteria for prophylactic medication. Berotralstat would offer this option to patients who suffer severe and debilitating attacks, often requiring hospital treatment, who currently are unable to have prophylactic treatment.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

The appropriate clinical trial evidence has been considered. The committee comments on the trial size, however, this would be commensurate with trials in rare diseases, where treatable populations are small and ability to recruit and randomise is challenging. The trials are consistent with other HAE therapeutics that have gone through the licensing process.

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

The clinical efficacy data from the trials is evident, with a significant reduction in attack frequency and no concrete data, but as a clinician with real life experience, I would note that patients attack severity has also diminished, which is a highly important factor in considering therapeutic options. The cost effectiveness is partly based on withdrawal if therapy is not effective for that individual. This would be routine counselling for a new high-cost therapy. The comment re: severity needs consideration - a patient who had ongoing minor, non treatable attacks of HAE, who had been getting severe life threatening episodes would be considered a treatment response and should continue, but patients with no significant alteration in attack frequency or severity should not continue therapy and this would be standard practice with the currently available options, mainly due to the toxicities of e.g. androgens which would not be continued if the patient was non-responsive. There should not therefore be a concern that individuals who do not benefit from the medicine are discontinued, since this would be good practice. Given the committees concern on the practicality of using a 50% reduction threshold to determine continuation of therapy, perhaps a clinically effective model (reduction in frequency and/or severity) would be appropriate, but clear guidance on discontinuation for sub-optimal response should be made.

I would query the assumptions or the basis of it for treatment associated costs (acute therapy). The experience of androgens and tranexamic acid in treating patients with HAE is that when effective they reduce the severity and/or frequency of attacks. Treatment of acute attacks tends to diminish because there are fewer severe treatable attacks and milder attacks tend to resolve more quickly and are less likely to require rescue second therapy/re-treatment, which would reduce the cost of acute therapy. With regards carer disutility, I would like to see a measure included. I care for a cohort of children at a children's hospital. Parents will have to take time off work or study and care for a sick child, with a recurring unpredictable disorder. The impact on carers is both economically and socially significant and it is appropriate to consider the impact of the therapy on a family.

In terms of clinical effectiveness and durability, my experience through the EAMS scheme has been that the efficacy of the therapy increases over time (progressively better control); I accept that this isn't obvious from the pivotal study, but would hope that the company can produce data that shows increasing efficacy over time. Even if the data is not available, those patients who lost benefit, would therefore fall under the failed efficacy clause and treatment would be withdrawn.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations as a prescribing clinician who is responsible for the care of children as well as adults with HAE are disappointing. Trials in HAE are small because it is a rare disease and so by definition if they meeting the criteria set out by regulators in the USA and Europe for marketing authorisation and have appropriate statistical validity, they should be sufficient to make a decision for the NHS on the validity of commissioning.

The recommendations do not seem to take into account that under the heading "inappropriate for androgen therapy" would include patients who are 12-18 years of age who are not appropriate to receive hormonal therapy. This falls within the remit of the marketing authority and this group of patients do not have a viable alternative therapy for prophylaxis. Tranexamic acid is used "off-label" in this group, with low efficacy and is rejected by some families because of the perceived risk of thrombosis. Androgens and progestogens are either medically inappropriate in this age group or declined because of the side effect profile by carers. The guidance at point 3.2 appears to be flawed, since, androgens are not suitable for patients who cannot medically be prescribed them or for whom the side effect profile is unacceptable, this falls within the proposed guidance that Berotralstat would be offered to those for whom androgens are inappropriate, I cannot therefore foresee a population group that would be denied therapy on this basis.

- 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?

I would note that children will be specifically disadvantaged if this therapy is not made available, the discrimination would be indirect, but since by virtue of age they are nearly always ineligible for androgens, and there are no licensed oral prophylactic therapies a negative decision would explicitly disadvantage/discriminate against this group where limited options may be available for older patients.

Name	[redacted]
Role	
Other role	
Organisation	Barts Health NHS Trust, Department of Immunology
Location	
Conflict	
Notes	

Comments on the ACD:

- Has all of the relevant evidence been taken into account?

My comments are informed by my experience of being the lead for HAE at Barts Health NHS Trust where the largest UK cohort of adults and children with HAE cared for. At Barts, we performed the clinical trials for Berotralstat and currently are treating 13 patients with Berotralstat on the EAMS scheme. I have been the principle and chief investigator for the Berotralstat clinical trials and other HAE drugs such as Lanadelumab or KVD-900. I am the senior author for the APEX-2 (48- weeks Berotralstat) and presented the 96- weeks data for Berotralstat in the European Academy of Allergy and Clinical Immunology (EAACI) congress 2021.

Real wold evidence (RWE) has been accumulating since the Early Access to Medicines Scheme for Berotralstat in February 2021. Approximately 100 patients in the UK are on Berotralstat through EAMS. We are collecting data on these patients through the UK HAE network. This could provide relevant evidence but are not included in this consultation.

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

No comments.

- Are the recommendations sound and a suitable basis for guidance to the NHS?

No comments

- 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?

No comments.

- Section 1 - recommendations

APEX-2 studied the effect of Berotrastat over a 48 weeks' period. Compared to other clinical trials for HAE, APEX-2 could be considered as a long trial. HELP study for Lanadelumab was conducted over a 26 weeks' period. The APEX-S study extended the use of Medication to 96 weeks demonstrating durability of the efficacy and a very good safety profile over the 96 weeks of the study. In our cohort of 13 patients who are being treated with Berotralstat we continue to observe the reduction in attack frequency and the number of attacks that require treatment (i.e reduction in attack severity)

Since HAE is a rare disease, inevitably the number of participants in clinical trials are low and this is the case for all HAE trials.
The effect of a drug on attack location and severity is indeed important and it was taken into account in the APEX-2 study as the number of attacks requiring treatment were measured which is a surrogate for attack severity and location. Please note that all above-neck attacks are considered to be more dangerous and should be treated.

- Section 3.2 - The company proposes that berotralstat is used after androgens, but this may prevent some people from accessing treatment

There is a considerable number of patients for whom prophylaxis is indicated but fall in between the group who are eligible to receive prophylactic C1- Inhibitor replacement therapy or Lanadelumab, and the group for whom prophylaxis is not indicate. These patients have no other choice apart from attenuated androgens (AAs) but AAs are not appropriate for all the members of this cohort.
Some patients may not wish to have androgens as they find the side effect profile unacceptable or AAs are contraindicated for them in which case their only choice of prophylaxis is Berotralstat provided they has access to it.

- Section 3.6 - The company's model structure is acceptable for decision making, but the continuation rule may not be appropriate in clinical practice

Attack frequency is a useful measure of disease control and is an indicator of attack severity. Patients with can have flares of disease during which attack severity and frequency increases. Reduction in attack frequency often occurs along with a reduction in attack severity. The commissioning guidelines for the use of C1-Inhibitor replacement or Lanadelumab recommend adjustment of frequency or dose of medication based on attack frequency.
It is important to note that a reduction in attack frequency that is less than 50% can be significant, if there are no other treatments that could achieve a better outcome. The decision of starting or stopping prophylaxis, in practice, is made jointly between a patient and a clinician. The primary factor that influences this decision is patient quality of life (QoL). The final decision is based on a combination of benefits, side effects, inconvenience of use, and whether any other alternative drugs exist that may provide better treatment.
In a survey of UK clinical immunologists that I also took part, the consensus was that the clinicians would consider changing prophylaxis if there was not a >50% reduction in attack rate after 3 months. This is a useful cut-off for the clinician to reassess the patient and decide together with the patient on continuation of the treatment. However if , despite a <50% reduction in attack rate, the patient reports a degree of improvement in QoL that could not be obtained by switching to any other available prophylactic medication, in practice, the current treatment would continue based on a patient-centred joint decision. The improvement in QoL could come from a reduction in attack severity, number of attacks requiring acute treatment or change in the location of swellings that could result in a reduction in the risk of asphyxiation.

In addition, having a cut-off point would also allow an opportunity to reassess patients for emergence of new factors contributing to HAE flares. e.g. are there underlying psychological or physical precipitating factors at this point of time which are contributing to the inadequate response to prophylaxis. Addressing these underlying factors could increase the magnitude of the response to prophylaxis.
Please note that it is now accepted knowledge that HAE severity changes with

physiological and psychological changes such as for instance colonisation with H pylori or going through a psychologically stressful period of time.

- Section 3.8 - It is uncertain how much berotralstat reduces attacks compared with standard care beyond the trial follow up period

Our real world experience at Bart Health with the 3 patients from the APEX-S study who have continued with medication through EAMS who have been on Berotralstat for >96 weeks now and patients who have been on EAMS from February 2021, shows that similarly to Lanadelumab in HELP-OLE studies, there is a progressive reduction in attack rates after a few months of treatment. This is interesting as both these medications target the same enzyme (Kallikrein). Clinically it appears that the contact system may reach a different level of equilibrium with time which results in lower frequency of attacks. From our RWE the disease in patients who do respond to Berotralstat seems to become progressively more stable wit time.

Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

ERG critique of the company response to the Appraisal Consultation Document (ACD)

Produced by: Aberdeen HTA Group

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University of Aberdeen, Health Economics Research Unit
Foresterhill, Aberdeen, AB25 2ZD
Email: g.scotland@abdn.ac.uk

Date completed: **5 August 2021**

Contains: **AIC /CIC**

Following the first appraisal committee meeting for this appraisal, the committee were minded to not recommend berotralstat within its marketing authorisation. The company provided a response to nine issues of concern raised by the committee (see the company's ACD consultation comments) and revised their economic model to address some of these concerns. In this document, the ERG provides comments on the company's response and their revised economic modelling. It should be read in conjunction with the company's response to the ACD. The focus is on the updates made to the economic model. The ERG has also provided a further cPAS appendix, which reproduces the company's revised analysis using confidential CMU prices that are available for the therapies used to treat angioedema attacks (Berinert, Cinryze, Ruconest and Firazyr).

Issue 1. Treatment pathway (positioning)

This issue relates to the concerns the committee had in relation to the company's proposed positioning of berotralstat, for people with at least 2 angioedema attacks per month who have used androgens before, or if androgens are unsuitable. The ACD refers to expert advice that the "*supply of androgens in the NHS is inconsistent. They explained that access to androgens is variable, is based on local arrangements and people are unable to get them from local pharmacies"* and that current Department of Health and Social Care advice to clinicians is "t*o not start prescribing androgens to people who have not had them before"*. The committee further noted that "*people under 18 cannot have androgens, but people under 18 are included in the marketing authorisation for berotralstat*". Thus, the committee were concerned that the positioning proposed by the company may inadvertently prevent some people from accessing berotralstat.

In response, the company note that it was intended that unsuitability for androgens would include people under the age of 18. They agree that it would be preferable to include people with two or more attacks per month who are denied access to treatment with androgens due to supply shortages. They have therefore revised the wording of their positioning as laid out in the ACD response document, to include unavailability as criteria for access.

ERG comment

The ERG agrees with the company that under 18s should be captured by the term unsuitable for androgens. The inclusion of unavailability of androgens as a criteria for access to berotralstat in the context of the current Department of Health and Social Care advice to clinicians on androgen prescribing, may substantially increase the eligible population compared to the wording of the previous positioning. This may add weight to the relevance of data from the wider subgroup of APeX-2, with two or more attacks per month at baseline (inclusive of those who have and have not previously used androgens).

Issue 2. Clinical issues (impact on severity unknown)

This point relates to the committee's discussion around the importance of attack severity as well as attack frequency, but a lack of evidence provided to support an effect of berotralstat on attack severity.

The company have agreed that attack severity is an important consideration in addition to attack frequency. The company claim their model accounts for severity by capturing attack location and duration as proxy measures for severity. They also point to the increased use of acute therapies per attack in the SoC arm as another indicator of attack severity.

The company point to data from the APeX-2 trial, which showed that berotralstat reduced the laryngeal attacks (potentially the most severe type of attack) by [redacted] compared to placebo ([redacted]). They further note evidence suggesting that berotralstat reduced attack duration in patients who transitioned from the placebo arm of the double blind phase of APeX-2 (Part 1) to berotralstat 150mg in the open label extension phase: from [redacted] to [redacted], a reduction of 8 hours.

ERG comment

The ad hoc analysis on laryngeal attacks, does suggest that berotralstat is effective in reducing these potentially severe types of attack, but the ERG is not convinced that this provides conclusive evidence that berotralstat reduces the severity of attacks compared to those that occur on SoC. The quoted effect on laryngeal attacks is a bit larger than the overall effect ([redacted] reduction). However, the numbers informing the analysis and the confidence interval for the estimate are not provided. In the subgroups informing the model, the proportional distribution of attack location by treatment arm is similar (e.g., [redacted] laryngeal attacks for berotralstat and [redacted] laryngeal attacks for placebo in the company's preferred subgroup, [redacted] versus [redacted] in the larger subgroup).

*With respect to the evidence presented to support an effect on duration, the ERG would note that the presented data are not from a randomised comparison. It is a before and after comparison for a subset (*n=17*) of the placebo group in phase 1 of APeX-2 who moved on to receive berotralstat 150mg in phase 2 (Wedner et al.*

2020).[1] The comparative data on attack duration from the placebo randomised phase of APeX-2 was reported to be [redacted] ([redacted]) for berotralstat versus [redacted] ([redacted]) for the placebo group. So overall, the ERG does not find the argument for a differential effect on attack location or duration to be very convincing based on the data from APeX-2, and suggest the data better supports a consistent effect on attack frequency across attack locations. The caveat to this is the impact on the reduced need for repeat doses of acute therapies per attack in the berotralstat arm of APeX-2. This could potentially explain the lack of effect seen on attack duration.

Issue 3. Application of a continuation rule in the model

The ACD describes the committee's concern that the continuation rule applied in the company's model may not be appropriate in clinical practice. The patient experts noted that reductions in the frequency of attacks of less than 50%, or impacts on severity, would be considered beneficial. From this, the ACD notes that the committee "*was concerned that it would be difficult to implement the continuation rule in clinical practice*".

The company's response notes that a continuation rule for berotralstat has already been implemented into NHS practice via the Blueteq system for those who have access through the Early Access to Medicines Scheme (EAMS). They further note support for the criteria of a 50% reduction applied at 3 months based on a delphi panel of 9 clinical experts. Finally, they note precedence for continuation rules being applied in hereditary angioedema, with the current C1-INH commissioning policy stating that: "*If treatment is ineffective after two months (defined as a lack of reduction in attack frequency despite optimised treatment) then treatment with prophylactic C1-inhibitor should be discontinued and alternative therapy options considered*" (NHS England, Specialised Commissioning Team, 2016).[2]

<u>ERG comment</u>

As indicated in the ERGs original report, the ERG's clinical expert advisor was broadly supportive of the proposed continuation rule applied in the company's model. The ERG would note, however, that the current wording for continuation of berotralstat in the EAMS scheme, or for C1-INHs in the C1-INH commissioning policy, do not strictly define what the appropriate percentage reduction in attack

frequency should be to warrant continuation. The company further note that this applies to a definition of clinically significant attacks as set out in the NHS C1-INH commissioning policy:

> "is *i) potentially life threatening because it affects the head or neck or ii) causes pain or disability such that the patient cannot continue their normal activities. This may be due to disabling cutaneous swelling, sufficient to prevent the patient from undertaking normal activities or severe abdominal pain which will not respond to oral analgesia. Varying treatment pathways do not imply that an attack requiring hospital treatment is necessarily more significant than one which can be treated with self-administered therapies*."

Issue 4. Small sample size in the base case subgroup

This point relates to the committee's discussion of the small subgroup of patients, best matching the company's proposed positioning, being used to inform the model inputs in the company's base case. Given the sample size limitations, and a lack of clear evidence to suggest that the data from a larger subgroup of patients experiencing $\geq$ 2 attacks per month at baseline would not be generalisable to the proposed positioning, the ERG suggested that analyses based on this larger subgroup were also relevant for consideration.

The company have reiterated their arguments that their preferred subgroup most closely matches their proposed positioning, as identified by clinical experts as the group with the greatest unmet need in NHS clinical practice. They also suggest this is the group in which berotralstat is most cost-effective and represents the most efficient use of NHS resources. However, the company have provided a scenario analysis using data from the larger (≥2 attacks per month) subgroup to address the committee's preference to consider results based on both subgroups.

ERG comment

The ERG agrees with the company's approach to present results based on both subgroups and considers that they are both relevant for consideration. The motivating factor for this is to reduce the chance of generating spurious findings due to small numbers. However, the ERG recognises the potential trade-off between increasing sample size and potentially reducing generalisability to the population that

will receive treatment if berotralstat is accepted. That said, the company claim that their amendments to the berotralstat positioning have no material impact on the data used to inform their model base case. The ERG has some reservations about this, as in the context of the limited androgen availability described by clinical experts (ACD), the change in wording to the positioning could include more patients who have not previously used androgens. As noted above, this may add weight to the relevance of data from the larger subgroup.

Issue 5. Extrapolation of berotralstat's efficacy in reducing attack rate compared with SOC beyond the observed trial period

This issue relates to the committee's discussion of the approach to extrapolate the effect of berotralstat versus SoC beyond the follow-up period of the trial, as set out in section 3.8 of the ACD. The company's base case at ACM1 carried forward the average percentage reduction in attack rate over months 4 to 12 for berotralstat and set the SoC attack rate to baseline beyond the end of follow-up (6 months) of the placebo arm of APeX-2. The company argues that any reduction in attack rate observed over months 1-6 in the relevant subgroups of the placebo arm of APeX-2 is a placebo effect that would not be seen in routine clinical practice under SoC. They correspondingly believe that the effect in the berotralstat arm is all attributable to the treatment and is durable as indicated by the ongoing decrease in the mean monthly attack rate beyond Month 6.

The ERG accepts that this may form part of the explanation for the observed pattern in the placebo arm of APeX-2, but also believes that some of the reduction in attack rate seen in the relevant subgroups of APeX-2 may be due to regression to the mean; i.e., patients experiencing a high attack frequency ($\geq$ 2 per month) during the screening period (maximum 10 weeks) were selected into the subgroups, and so some of the reduction in subsequent months may reflect regression to the mean. Under this explanation, the average reduction across months 0-6 in the placebo arm may give a better indication of the average expected attack rate going forwards beyond month 6. Similarly, part of the reduction seen in the berotralstat arm may also be due to this same effect.

The company in their response have provided newly published 96-week data on the monthly attack rate for the berotralstat arm of the APeX-2 trial (Kianie et al., 2021)[3] They note that the benefit with berotralstat increased over time, with the mean monthly attack rate generally decreasing steadily from month 1 through to month 24. They state that this gives confidence that the berotralstat treatment effect is not related to a placebo effect. The 24-month data are included in the revised model, whereby observed monthly percentage reductions in attack rate from baseline are applied up to month 24, and thereafter the average percentage reduction through months 4-24 is carried forwards.

The company further note that clinical experts they consulted at an advisory board expected the placebo effect to wear off after several months. Therefore, to address the committee's concern, the company have provided a more conservative extrapolation of the percentage reduction in attack rate for the SoC arm, whereby the observed percentage reduction in monthly attack rate is applied through months 1-6, and then the average reduction over months 1-6 returns linearly to 0% over months 7-12.

ERG comment

The ERG is generally satisfied with the company's approach to modelling the percentage reductions in attack rate in the berotralstat arm. However, it should be noted that there is substantial attrition in the number informing the monthly percentage reductions over time. If those with poorer response are more likely to be lost to follow-up, this may partly explain the apparent downward trajectory in monthly attack rates with increasing length of follow-up (see Figure 2 in the Appendix to the company's response to the ACD). In this respect, the company's decision to apply flat averages rather than weighted averages (accounting for numbers of observations) for extrapolating the percentage reduction in monthly attack rates could generate bias, although scenario analysis indicates the impact is minimal (see scenarios 5-9 below). The company have not presented the data for the group that have been fully observed over the entire 96-week follow-up period. Further, for the responder groups, there is less obvious support for a continued decline in average monthly attack frequency beyond month 3 when response status is assessed.

The company's revised approach in the SoC arm seems somewhat irrelevant in the context of their favoured explanation for the reduction/variability in attack rate observed in the placebo arm of APeX-2. If they argue that it is purely due to placebo effect, and ultimately carry the baseline attack rate forwards as a true representation of the average monthly attack rate, then they would be as well to apply it from the start of the model (i.e., in routine practice there would be no placebo and increased contact, so no reductions in attack rate). However, if the reductions/variability in the placebo arm of APeX-2 reflects, or partly reflects, regression to the mean, then carrying forward the average attack rate through months 0-6 is a relevant scenario for consideration alongside one that applies the baseline attack rate in the SoC arm. The ACD noted that it may be more appropriate to subtract the average percentage reduction in the placebo arm of the trial from the average percentage reduction in the berotralstat arm for extrapolation. This is similar to carrying forward the average percentage reduction in the SoC arm, for which the ERG presented scenarios following technical engagement, but retains the baseline attack rate in the placebo arm. This is akin to applying the placebo controlled relative reduction from baseline forwards in the model. The ERG includes this as a scenario (scenario 3 below) and suggests that both the company's original scenarios and this alternative should be considered to address the range of uncertainty associated with extrapolation. A further scenario (scenario 4) is also included which removes 50% of the average percentage reduction in the placebo arm of APeX-2 from the percentage reduction in the monthly attack rate in the berotralstat arm beyond 6 months, thus providing a middle ground between the alternative scenarios.

Issue 6. The committee's interest in capturing utilities by attack severity in the model

This issue relates to the concern that the utility values included in the model do not adequately capture attack severity. It was noted that this issue applies to both the utility values from Nordenfelt et al. study[4] used in the company's base case and those derived from EQ-5D data collected in APeX-2. The ACD states the committee concluded that *"additional analysis using utility values that reflect attack severity as well as attack rate reduction would be preferable."*

In their response, the company agree that reducing attack severity is an important outcome for patients but argue that the model already captures the impact of berotralstat on attack severity through the cost calculations where attack location, attack duration and the need for acute therapies were used to estimate treatment arm specific attack costs. The company also highlight that as the attack disutility is applied for the duration of each attack, this will also capture the impact of berotralstat on attack severity with a shorter mean attack duration applied in the berotralstat arm based on APeX-2 data ([redacted] vs [redacted] in the berotralstat and placebo arms respectively in the smaller subgroup). To explore this further, a scenario analysis is also provided where an administration disutility is included to capture the quality of life impact of berotralstat in reducing the need for acute therapies.

ERG comment

As described in response to Issue 2 above, the ERG does not believe a strong case has been presented to support a treatment effect with berotralstat on reducing attack severity. The ERG agrees with the company's view that, although there are limitations with the data sources used to estimate utility values, the model adequately captures any potential impact of berotralstat on severity through the lower cost of attacks and the shorter duration of attacks observed in APeX-2. To include an additional utility benefit with berotralstat also assumes that the Nordenfelt et al. study[4] and the APeX-2 data do not capture the impact of severity on quality of life and may overestimate the treatment effect given the lack of robust evidence to support this potential additional benefit. Another proxy for attack severity is attack location (with laryngeal attacks considered the most severe), and evidence from APeX-2 shows a similar distribution across both the berotralstat and placebo arm attacks indicating limited evidence of an additional effect on attack location.

Issue 7. Inclusion of caregiver quality of life effects in the base case

This issue relates to the inclusion of a carer disutility for 52.4% of attacks based on a burden of illness study. The ACD describes the committee's concern that there is no clear evidence to justify the inclusion of caregiver disutilities in the context of other appraisals in this disease area and the quality of life impact on carers due to displaced treatments. The committee concluded that it was not appropriate to include caregiver quality of life effects in the model base case.

In their response, the company acknowledge other HAE appraisals do not apply a caregiver disutility but also reiterate their argument that there is a burden on caregivers. The company also argue the approach they have used is conservative and describe an alternative method of applying a caregiver disutility in the model. Despite this, the company agreed that it is more appropriate to consider a carer disutility as a scenario analysis.

ERG comment

The ERG notes the points raised by the company in relation to the inclusion of a carer disutility and in particular the method used to apply this in the model. The company describe an alternative approach where a caregiver disutility is applied to all attacks requiring acute treatment, resulting in a greater impact on the model with a disutility applied to [redacted] *and* [redacted] *of attacks in the SoC and berotralstat arms respectively. The ERG notes that no evidence is provided to show that all attacks requiring acute treatment have a quality of life impact on caregivers. Other more conservative methods could also be relevant, such as applying carer disutilities to only laryngeal attacks (as a proxy for severity), or attacks requiring repeat administrations of acute treatment. There is considerable uncertainty associated with the scenario analysis provided and other more conservative methods could have been explored. Given the lack of evidence to support its inclusion, the ERG agrees with the committee that carer disutility is not appropriate for consideration in the base case analysis.*

Issue 8. Uncertainty in the cost-effectiveness estimates

This issue relates to the uncertainty in the cost-effectiveness estimates and that some clinically plausible scenarios result in incremental cost-effectiveness estimates above £20,000 per QALY gained.

In their response, the company acknowledges the issues raised and highlight the changes made to the base case assumptions to reduce uncertainty in the model. Additional data are provided up to 96-weeks from APeX-2 alongside real-world evidence gathered as part of EAMS. The company also provided an updated PSA.

ERG comment

The ERG notes the changes made to the model base case to address some of the key issues raised in the ACD. However, there remain some important uncertainties in the model, in particular in relation to the attack rate extrapolation assumptions applied in the SoC arm and the choice between the smaller and larger subgroups for use in the model. These unresolved issues mean the model results are still uncertain with a number of estimates above £20,000 per QALY gained (see confidential appendix).

The company also provided an updated PSA, whereby normal distributions are applied to the percentage changes in monthly attack frequency from baseline. However, these are still constrained to be either below zero or above zero depending on the direction of the point estimate, and the assumed standard error is correlated with the magnitude of the point estimate, potentially underestimating the uncertainty around smaller percentage changes in the SoC arm.

Issue 9. Innovation

The ACD acknowledges that berotralstat is an innovative treatment as it is the first licensed oral prophylactic treatment for recurrent attacks of HAE but the committee concluded that all relevant benefits are already captured in the cost-effectiveness estimates.

In their response to this point the company reiterate that they consider the oral formulation of berotralstat to be an additional benefit given acute therapies require subcutaneous or intravenous injections. The company summarise evidence from 3 studies selected non-systematically showing patient preference for non-invasive treatments, utility benefits associated with oral treatments and difficulties associated with treatments requiring a peripheral vein to administer. Given this, the company provides a scenario analysis on the revised base case (already provided as a scenario analysis in their initial evidence submission) where an additional utility decrement is included for attacks requiring acute treatment.

ERG comment

The ERG previously commented on this scenario analysis exploring the impact of increasing the attack disutility due to the use of treatments that require subcutaneous or intravenous administration. This assumes the Nordenfelt et al. study[4] does not capture the quality of life impact of requiring subcutaneous or intravenous treatments for acute attacks. The ERG would also like to highlight again the magnitude of utility decrement applied in this scenario analysis (-0.147) compared to the utility increment applied to the lanadelumab arm of TA606 (0.024). The ERG agrees with the company that the impact of mode of administration on quality of life should not be included in the base case analysis.

ERG scenario analysis with the company's revised model

To further explore uncertainty around the company's revised base case, the ERG has conducted some further scenario analyses based on inputs from both the smaller and larger subgroups of APeX-2. Table 1 provides the results for the smaller subgroup (≥2 attacks per month and previous use of androgens and baseline), and Table 2 provides the results based on inputs from the larger subgroup (≥2 attacks per month). The scenarios are as follows:

- Scenario 0 reflects the company post-ACD revised base case settings
- Scenario 1 applies the company's previous extrapolation assumption for SoC, of setting the attack rate equal to baseline beyond 6 months (end of follow-up for the placebo arm of APeX-2)
- Scenario 2 applies the ERG's previous alternative approach of carrying forward the average monthly attack rate over months 0-6 in the placebo arm of APeX-2 beyond 6 months
- Scenario 3 applies the committee suggested alternative approach of removing the average percentage reduction in the placebo arm of APeX-2 from the percentage reduction in the monthly attack rate in berotralstat arm beyond 6 months
- Scenario 4 removes 50% of the average percentage reduction in the placebo arm of APeX-2 from the percentage reduction in the monthly attack rate in berotralstat arm beyond 6 months (providing a middle ground between scenario 1 and scenario 3)

Scenarios 5-9 mirror those in 0-4 but differ in that they apply weighted averages for calculating the mean percentage reductions in monthly attack rates, based on the number of observations available at each time point.

Table 2 mirrors Table 1, but with the model inputs being based on the larger subgroup of APeX-2 (≥2 attacks per month).

Note, all scenarios use the 24 months data for berotralstat, and beyond 24 months carry forward the average (or weighted average) percentage reduction in monthly attack rate across months 4-24.

Table 1 ERG's further analysis around the revised company base case using inputs from the smaller subgroup (≥2 attacks per month and previous use of androgens and baseline) [revised berotralstat PAS (July 2021) and list prices on acute therapies]

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
0	**Company Base Case (July 2021)**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
	ERG further analyses							
1	**SoC: Baseline attack rate carried forward beyond 6 months**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
2	**SoC: average attack rate over months 0-6 to carried forward beyond 6 months**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
3	**SoC: Baseline attack rate carried forward beyond 6 months; Berotralstat: placebo average percentage reduction removed from the berotralstat average percentage reduction from month 7**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
4	**SoC: Baseline attack rate carried forward beyond 6 months; Berotralstat: 50% of placebo average percentage reduction removed from the berotralstat average percentage reduction from month 7**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
5	**Company base case but using weighted average percentage reduction in attacks for extrapolation**							
	SoC	[redacted]	[redacted]	[redacted]				

	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
6	**Weighted average percentage reduction in attacks used for extrapolation; SoC: Baseline attack rate carried forward beyond 6 months**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
7	**Weighted average percentage reduction in attacks used for extrapolation; SoC: weighted average attack rate over months 0-6 to carried forward**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
8	**Weighted average percentage reduction in attacks used for extrapolation; SoC: Baseline attack rate carried forward beyond 6 months; Berotralstat: placebo weighted average percentage reduction removed from the berotralstat weighted average percentage reduction from month 7**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
9	**Weighted average percentage reduction in attacks used for extrapolation; SoC: Baseline attack rate carried forward beyond 6 months; Berotralstat: 50% placebo weighted average percentage reduction removed from the berotralstat weighted average percentage reduction from month 7**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant

Table 2 ERG's further analyses using data inputs from the larger subgroup (≥ 2 attacks per month at baseline) [revised berotralstat PAS (July 2021) and list prices on acute therapies]

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
0	**Company Base Case settings (July 2021)**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
	ERG further analyses							
1	**SoC: Baseline attack rate carried forward beyond 6 months**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
2	**SoC: average attack rate over months 0-6 to carried forward beyond 6 months**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	107,350
3	**SoC: Baseline attack rate carried forward beyond 6 months; Berotralstat: placebo average percentage reduction removed from the berotralstat average percentage reduction from month 7**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	56,683
4	**SoC: Baseline attack rate carried forward beyond 6 months; Berotralstat: 50% of placebo average percentage reduction removed from the berotralstat average percentage reduction from month 7**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
5	**Company base case settings but using weighted average percentage reduction in attacks for extrapolation**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant

6	**Weighted average percentage reduction in attacks used for extrapolation; SoC: Baseline attack rate carried forward beyond 6 months**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
7	**Weighted average percentage reduction in attacks used for extrapolation; SoC: weighted average attack rate over months 0-6 to carried forward**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	110,766
8	**Weighted average percentage reduction in attacks used for extrapolation; SoC: Baseline attack rate carried forward beyond 6 months; Berotralstat: placebo weighted average percentage reduction removed from the berotralstat weighted average percentage reduction from month 7**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	59,710
9	**Weighted average percentage reduction in attacks used for extrapolation; SoC: Baseline attack rate carried forward beyond 6 months; Berotralstat: 50% of placebo weighted average percentage reduction removed from the berotralstat weighted average percentage reduction from month 7**							
	SoC	[redacted]	[redacted]	[redacted]				
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant

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