Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

Produced by Aberdeen HTA Group

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Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contribution of authors

Clare Robertson and Miriam Brazzelli summarised and critiqued the company's definition of the decision problem and the clinical effectiveness evidence reported within the company submission. Dolapo Ayansina critiqued the statistical methods and analyses presented in the company submission

and checked all the numerical results related to the review of the clinical effectiveness evidence. Corinne Booth, Rodolfo Hernandez and Graham Scotland critiqued the cost-effectiveness evidence submitted by the company, checked their economic model, and conducted further sensitivity analyses. Paul Manson critiqued the methods used for identifying relevant studies and checked the search strategies presented in the company submission. Richard Herriot provided clinical advice during the appraisal. Miriam Brazzelli acted as lead for the clinical effectiveness side of the appraisal. Graham Scotland coordinated all aspects of the appraisal and acted as lead for the cost-effectiveness side of the appraisal. All authors contributed to the writing of this report and approved its final version.

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AE-QoL	Angioedema Quality of Life Questionnaire
BNF	British National Formulary
C1-INHs	C1-esterase inhibitors
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CS	Company submission
EAMS	Early Access to Medicines Scheme
ERG	Evidence review group
EQ-5D-5L	EuroQol 5-Dimensional 5-Level Questionnaire
EU	European Union
HAE	Hereditary angioedema
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
MCID	Minimal clinically important difference
MHRA	Medicines & Healthcare products Regulatory Agency
NHS	National Health System
QALY	Quality-adjusted life year
QoL	Quality of life
PIM	Promising Innovative Medicine
PSSRU	Personal Social Services Research Unit
RCT	Randomised controlled trial
SAEs	Serious adverse events
SOC-Rx	Standard of care acute attack medication
TEAEs	Treatment-emergent adverse events

Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the main aspects of the company submission and ERG's key issues

The company submission (CS) focuses on berotralstat for hereditary angioedema. In a deviation from the NICE scope, the CS focuses on standard of care (use of on demand therapy) as the sole comparator treatment.

The key clinical effectiveness evidence is provided by one Phase III randomised, double-blind, placebo-controlled multi-centre trial. Participants were randomised 1:1:1 to either 110mg berotralstat (n=41), 150 mg berotralstat (n=40), or placebo (n=40). The company state that the 110mg dose of berotralstat is not clinically relevant to this submission as this dose will not be marketed in the UK, and does not present results for this treatment dose in the CS. The CS, therefore, considers data for 40 participants randomised to 150 mg berotralstat and 40 participants randomised to placebo. The primary efficacy endpoint of APeX-2 was the rate of investigator-confirmed HAE attacks during the Part-1 treatment phase (day 1 to week 24). The secondary endpoints were: change from baseline in Angioedema Quality of Life Questionnaire (AE-QoL) total score at week 24 (the minimal clinically important difference [MCID) is -6); the number and proportion of days with angioedema symptoms through the 24-week treatment period; the rate of investigator-confirmed during dosing in the effective treatment period. Safety

outcomes included: treatment-emergent adverse events (TEAEs); discontinuation due to TEAEs; treatment-emergent serious adverse events (SAEs); Grade 3 or Grade 4 TEAEs. The company did not conduct a meta-analysis or indirect treatment comparison.

Orphan designation (EU/3/18/2028) for the use of berotralstat for treating hereditary angioedema was granted to BioCryst UK Ltd, UK by the European Commission on 27 June 2018. An application is under evaluation by the Committee for Medicinal Products for Human Use (CHMP) for berotralstat as a new human medicine with approval expected in Q2, 2021. The Medicines & Healthcare products Regulatory Agency (MHRA) granted berotralstat Promising Innovative Medicine (PIM) status on 18 May 2018 and Early Access to Medicines Scheme (EAMS) status on 30 October 2020.

Table 1 presents a summary of the key issues identified by the ERG.

Table 1. Summary of the key issues

Issue number	Summary of issue	Report sections
Issue 1	Limited evidence base	3.2.1, 3.3 and 3.6
Issue 2	Selection of data used to inform the model inputs	4.2.6, 4.2.8
Issue 3	Extrapolation of attack rates beyond the follow-up period of the trial	4.2.6
Issue 4	Characterizing uncertainty around the ICER (PSA)	4.2.6
Issue 5	The use of utility values from a published study in preference to EQ-5D data collected in the APeX-2 trial	4.2.7
Issue 6	The inclusion of carer disutility in the base case analysis	4.2.7
Issue 7	The attack costs applied in each arm	4.2.8

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An incremental cost-effectiveness ratio (ICER) is the ratio of the extra cost for every QALY gained. In the current appraisal, a cost-effectiveness analysis was presented comparing 150mg berotralstat prophylaxis for HAE attacks to SoC (treatment on demand for acute attacks). The model inputs were based primarily on data from the APeX-2 trial.

Overall, the technology is modelled to affect QALYs by reducing HAE attacks which adversely affect the quality of life of patients and carers.

Overall, the technology is modelled to affect costs as a result of ongoing acquisition costs, and effects on the frequency of HAE attacks, which are associated with acute treatment costs and health care resource use.

1.3 The decision problem: summary of the ERG's key issues

Although, the CS addresses a narrower population and a narrower selection of outcomes than those specified in the NICE final scope, and focuses on standard care as comparator intervention, the ERG agrees with the rationale and justification provided by the company and does not have any key issue of concern related to the decision problem (see Table 3 in Chapter 2 for further details).

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG's key issue that relates to the clinical effectiveness evidence is detailed below (Issue 1).

Issue 1. Limited evidence base

Report section	3.2.1, 3.3 and 3.6
Description of issue and why the ERG has identified it as important	The main source of clinical evidence submitted by the company is a single trial (APeX-2) with a total of 80 participants. Primary outcomes are assessed at 24 weeks. The ERG has some concern that the current evidence of clinical effectiveness is based exclusively on a single trial with small sample size and a limited follow-up period.
What alternative approach has the ERG suggested?	The ERG does not have a suggested alternative methodology as this issue related to the current availability of data and not to methods.
What is the expected effect on the cost-effectiveness estimates?	The sample size issue is exacerbated in the cost-effectiveness analysis as the model inputs are derived from a subgroup of the overall trial population who meet the criteria for the company's proposed positioning.
What additional evidence or analyses might help to resolve this key issue?	The ERG acknowledges that without further data from RCTs, this issue cannot be resolved.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

The ERG's key issues that relate to the cost-effectiveness evidence are detailed below (Issues 2-7).

Issue 2: Selection of data used to inform the model inputs

Report section	4.2.6 (Treatment effectiveness and extrapolation)
Description of issue and why the ERG has identified it as important	The model is driven by percentage reductions from baseline attack rates for berotralstat and SoC patients, derived from the berotralstat 150mg and the placebo arms of APeX-2, respectively. Rather than deriving these inputs from the ITT population, the company base case uses the subgroup of patients in APeX-2 meeting the criteria of the company's proposed positioning: those who experienced an attack rate of ≥ 2 attacks per month during the screening period (14-56 days) prior to randomisation, and who had previously used androgens at baseline. This results in the model inputs being based on data from a small number of patients (n=35, 17 berotralstat patients and 18 SoC patients). Furthermore, since the model applies a treatment continuation rule in which only those who experience a 50% or greater reduction in attack rate by 3 months continue berotralstat, the number of patients informing the longer-term percentage reduction in attack rates for berotralstat is further reduced (n=[redacted]). This leads to uncertainty around the percentage reductions applied, to which the model results are sensitive.

What alternative approach has the ERG suggested?	The ERG suggested that using data from the larger trial population would make better use of the available data and reduce uncertainty driven by the small patient numbers. This would rely on the assumption that percentage reductions in attack rate observed for the ITT population are generalizable to the sub-population experiencing a higher baseline attack rate with prior experience of androgens. The company instead provided scenarios in response to the clarification letter, using data from the larger subgroup of patients from APeX-2; those experiencing ≥ 2 attacks per month at baseline, inclusive of those with no prior experience of androgens (n=[redacted]). This may offer a more appropriate scenario, as it only requires the assumption that percentage reductions are generalizable between those with and without prior androgen experience. The company retain a preference for basing the clinical inputs in their model on the more restricted subgroup which is closest to the criteria of the proposed positioning for berotralstat. The ERG believes that using data from the larger subgroup may be preferable, as this increases the numbers of patients and events available to inform percentage reductions and other model inputs. The ERG also believes that data from the larger subgroup should be generalizable to those with prior androgen experience.
What is the expected effect on the cost-effectiveness estimates?	Basing the model inputs on data for the larger subgroup substantially increases the ICER.
What additional evidence or analyses might help to resolve this key issue?	The company have provided the additional data and scenarios required. What would help is clinical expert opinion on the generalizability of percentage reductions in attack rate between those with and without prior experience of androgens.

	An alternative (related to issue 3 below) would be to provide a model that utilises relative treatment effects (rate ratios) for berotralstat versus SoC (placebo). However, this approach is complicated by the use of a continuation rule, meaning that a rate ratio would have to be estimated for responders versus SoC (placebo). However, assuming relative treatment effects are generalisable, it could provide a more flexible approach for modelling cost-effectiveness by any baseline attack rate. It could also allow for uncertainty to be more accurately characterised in the probabilistic sensitivity analysis (see issue 3).

Issue 3: Extrapolation of attack rates beyond the follow-up period of the trial

Report section	4.2.6 (Treatment effectiveness and extrapolation)
Description of issue and why the ERG has identified it as important	To inform monthly percentage reductions in attack rates from baseline to 12 months for berotralstat, and out 6 months for SoC, the company used observed data for the subgroup of APeX-2. Beyond this they used the last observed percentage reduction carried forward over the remaining time horizon of the model. The ERG is concerned that:1) the company's approach uses treatment arm specific baseline attack rates, rather than adjusting for these and setting them equal between the arms; 2) percentage reductions for responders (n=[redacted]) were calculated relative to the average baseline attack rate for the wider subgroup (n=17), rather than the baseline attack rate of responders; and 3) Applying the last observation carried forward fails to recognise the observed variation in monthly attack rates compared to baseline and may by chance (particularly given the small numbers) exaggerate the expected difference in the attack rate between the berotralstat and SoC arms over the extrapolation phase of the model.
What alternative approach has the ERG suggested?	To address potential for bias in the context of the company's model, the ERG suggests an approach that: 1) sets the baseline attack rates equal between the arms; 2) calculates and applies mean percentage reductions for responders relative to the baseline attack rate of the responders (n=[redacted]); and 3) carries forward the average percentage reduction in the monthly attack rate rather than the last observation (averaging across months 4-12 for berotralstat responders, and months 0-6 for SoC patients).

	The company argue that it is inappropriate to use the average reduction from baseline attack rate in the placebo arm of APeX-2 for extrapolation, as they suggest that the patients in APeX-2 experienced a placebo effect that the led to observed reductions in months 1 to 5 of the trial, which had worn off by month 6. The ERG believes the reductions in months 1-5 in the placebo arm of APeX-2 may represent natural variation given the small sample, and are relevant for informing the average attack rate for SoC beyond the follow-up period.
What is the expected effect on the cost-effectiveness estimates?	The different changes proposed by the ERG have varying effects on the ICER. Combined they increase it. It is primarily the averaging of percentage reductions from the baseline attack rate (for extrapolation) that drives the increase.
What additional evidence or analyses might help to resolve this key issue?	Further clinical expert opinion or evidence offering support or otherwise for: 1. the alternative extrapolation options in the SoC arm of the model: a) The last observed percentage reduction from the baseline attack rate in the placebo arm of APeX-2 carried forward; b) the average monthly percentage reduction from the placebo arm baseline attack rate carried forward, or c) the baseline attack rate from the placebo arm carried forward 2. the alternative extrapolation options in the berotralstat arm of the model: a) The last observed percentage reduction from the baseline attack rate for berotralstat responders carried forward; or b) the average monthly attack rate observed over months 4-12 for berotralstat responders carried forward.

Issue 4: Characterizing uncertainty around the ICER (PSA)

Report section	4.2.6 (Treatment effectiveness and extrapolation)
Description of issue and why the ERG has identified it as important	The original probabilistic sensitivity analysis provided by the company used 10% of the mean percentage reductions in attack rates to represent standard errors for these parameters, rather than actual standard errors based on the data used. Given the small number of patients and events informing these inputs, the ERG was concerned that the approach would substantially underestimate the decision uncertainty.
What alternative approach has the ERG suggested?	The ERG suggested that the company provide a scenario in which the standard errors were based on the data, which the company provided at the clarification stage. However, the company argue that the amended distributions result in implausible variation in attack rates between the arms, which skews the ICER and biases against berotralstat. The ERG acknowledges that this may be true and that the problem may be due to the small numbers combined with a lack of correlation between the attack rate distributions applied in each treatment arm of the model.
What is the expected effect on the cost-effectiveness estimates?	This is uncertain, but the ERG is concerned that the company's original PSA underestimates the decision uncertainty and that the alternative may bias the ICER.
What additional evidence or analyses might help to resolve this key issue?	The uncertainty might have been better represented with a model that used relative treatment effects for berotralstat and berotralstat responders versus placebo. The attack rates for those on berotralstat could then be modelled relative to the attack rate in SoC arm. Using the output of a regression with adjustment for baseline attack rate, the treatment effect distributions could have been correlated with the distribution for the constant term (representing the mean estimated attack rate in the placebo arm).

Issue 5: The use of utility values from a published study in preference to EQ-5D data collected in the APeX-2 trial

Report section	Section 4.2.7 (Health related quality of life)
Description of issue and why the ERG has identified it as important	EQ-5D-5L data were collected in APeX-2 but were not used to estimate utility values in the model. The company highlighted limitations with the data, including the unpredictability of HAE attacks and insensitivity of the generic EQ-5D measure meaning they considered the data unsuitable for use in the model. Instead, the company selected a published study (Nordenfelt et al 2014) where vignettes were used to describe HAE attack health states to Swedish patients and then EQ-5D questionnaires were completed to capture QoL 'today' and based on their last HAE attack. The ERG believes the use of EQ-5D in APeX-2 should have been explored more thoroughly given these data are collected directly from patients in the APeX-2 trial, which is the main data source for the other key inputs in the economic model. The decision to exclude these data in favour of a separate published study is not adequately justified based on the evidence presented by the company.
What alternative approach has the ERG suggested?	During the clarification process, the company was asked to provide further detail on the EQ-5D scores and number of associated attacks. In their response the company provided EQ-5D scores for the subgroup of patients with ≥2 attacks per month and prior androgen use only, split by whether or not an attack was ongoing at the time of assessment. The company reiterated their view that the EQ-5D data did not capture the QoL impact of either the 'attack' or the 'attack-free' health states in the model due to the small patient numbers in whom an attack was ongoing and the 'unrealistic' results observed in the subgroup. Given the concerns with the robustness of the data due to small patient numbers in the subgroup, the ERG considers that it would be appropriate to explore using the full ITT EQ-5D-5L dataset to estimate utility values for patients in the 'attack-free' and 'attack' health states.
What is the expected effect on the cost-effectiveness estimates?	As the company did not present the EQ-5D data based on the ITT population, the impact on the ICER of using these data is currently unknown.

What additional evidence or analyses might help to resolve this key issue?	To explore the feasibility of using the EQ-5D-5L data from the ITT population in APeX-2 to estimate 'attack-free' and 'attack' utility values, the information provided in response to question B12, Table 16 from the clarification questions should be provided for the full ITT population. Regression analysis could be used to estimate an average 'attack free' and 'attack' utility.

Issue 6: The inclusion of a carer disutility in the base case analysis

Report section	Section 4.2.7 (Health related quality of life)
Description of issue and why the ERG has identified it as important	The company made the case that the carers of patients with HAE are impacted during an attack and included a caregiver disutility to account for this. This was based on an estimate of caregiver disutility from a company TTO study ([redacted]) which was said to reflect the impact on caregivers' QoL due to anxiety and the need to provide physical assistance during attacks. This disutility was applied in the model for all time spent experiencing an attack in the alive health state for all patients in each cycle. However, the ERG does not believe a strong case was made to include a carer disutility in the model. As berotralstat reduces the number of attacks, including this carer disutility reduces the QALYs in the SoC arm of the model, more than it does in the berotralstat arm.
What alternative approach has the ERG suggested?	The ERG agrees it is reasonable to consider the QoL impact of HAE attacks on carers, but does not consider a strong case has been made to include these data in the base case analysis. The magnitude of carer disutility ([redacted] per attack) also seems large when compared to the range identified in the DSU review of NICE TAs (0.01 to 0.173 per year). Given these uncertainties, the ERG believe that the removal or reduction of carer disutility represent relevant scenarios.
What is the expected effect on the cost-effectiveness estimates?	At the clarification stage, the company was asked to provide the results with carer disutility excluded. This increased the company ICER from £20,721 to £27,461
What additional evidence or analyses might help to resolve this key issue?	The ERG would welcome further evidence to justify the inclusion of carer disutilities. In addition, as the ERG considers the application of a single carer disutility for every attack too simplistic, additional

	justification for the assumptions used to apply carer disutility would be helpful.

Issue 7: The attack costs applied in each arm

Report section	Section 4.2.8 (Resources and costs)
Description of issue and why the ERG has identified it as important	The cost per attack is estimated to be higher in the SoC arm, which the company said was due to the reduced need for multiple administrations of acute treatments in the berotralstat arm compared with SoC. As there are more attacks in the SoC arm, a higher cost increases the overall attack cost relative to the berotralstat arm. However, the ERG's clinical advisor did not identify a plausible clinical reason for prophylactic treatment to consistently or predictably impact on the cost of treating attacks. It is possible that the different costs in each arm arising from the use of the APeX-2 acute treatment distribution is due to random variation because of the small patient numbers in the subgroup used to inform the model (n=35 patients: 17 berotralstat, 18 SoC [redacted]).
What alternative approach has the ERG suggested?	In the absence of robust evidence to support differing costs, the ERG considers a more plausible approach would be to estimate the cost per attack pooled across the treatment arms.
What is the expected effect on the cost-effectiveness estimates?	The ERG conducted an analysis which equalised the attack costs across the treatment arms which substantially increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	The ERG acknowledges there remains uncertainty around this parameter and would welcome further evidence to demonstrate the impact of better prophylactic treatment in reducing the cost of treating acute attacks. Using data from the ITT population would increase the sample size and potentially provide more robust data. Further clinical opinion on the use of multiple doses to treat acute attacks would also be helpful.

1.6 Summary of ERG's preferred assumptions and resulting ICER

Following the company's correction of a minor data input error, and the ERGs correction of an inconsistency in carer QALY formula for those on berotralstat, the ERG prefers the following assumptions:

1. Equalised baseline attack rates ([redacted] per month for the berotralstat and placebo arm)
2. Calculation of percentage reductions for responders relative to the baseline attack rate for responders, but applied to the fixed baseline attack rate for the subgroup as a whole (from month 4)
3. Average percentage reduction from baseline attack rate observed between months 4 and 12 for berotralstat responders carried forward beyond month 12 ([redacted])
4. Average attack rate over months 0-6 carried forward for SoC beyond month 6 ([redacted] from baseline)

The impact of each individual change is documented in Table 2. These results are not appropriate for decision making as they do not include the discounted prices available for the treatments used for acute attacks. A confidential appendix with the appropriate discounted prices will be provided for the committee.

Table 2 Summary of the ERGs preferred assumptions and ICER

Scenario	Incremental cost (berotralstat versus SoC)	Incremental QALYs (berotralstat versus SoC)	ICER (change from company base case)
Company original base case	[redacted]	[redacted]	20,707
Company base case (corrected for minor bugs)	[redacted]	[redacted]	21,129
1. Equalisation of baseline attack rates in the model	[redacted]	[redacted]	Berotralstat dominant
Berotralstat: application of percentage reductions for responders relative to the baseline attack rate for responders (from month 4)	[redacted]	[redacted]	20,786
Berotralstat: average attack rate between months 4 and 12 for responders to be carried forward	[redacted]	[redacted]	61,743
SoC: average attack rate over months 0-6 to be carried forward	[redacted]	[redacted]	182,524
ERG base case	[redacted]	[redacted]	160,308

Further uncertainties relating to cost of treating and managing acute attacks, the inclusion of and assumptions around the application carer disutilities, and the subgroup of the APeX-2 trial selected to inform the model inputs, lead to further upward uncertainty on the ICER. This is illustrated in further scenario analysis proved by the company and the ERG.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for this submission is hereditary angioedema (HAE). The company's description of the prevalence, symptoms and complications of HAE is generally accurate and in line with the decision problem. The relevant intervention for this submission is Berotralstat for the prevention of attacks of HAE.

2.2 Background

HAE is a rare genetic disorder that affects between 1 in 50,000 to 1 in 100,000 people in the UK and is characterized by recurrent and unpredictable attacks of angioedema affecting the subcutaneous tissues, airway and small bowel.[1] There are three types of angioedema designated as having a hereditary basis.[2, 3] Types I and II are due to genetic mutation in SERPING1, are clinically identical, and account for the great majority of cases of HAE cases (Type I accounts for ~85% of all HAE cases and Type II accounts for ~15% of all HAE cases). Type III HAE is associated with normal C1-INH and is much rarer than Types I and II.[4] The company submission focuses on Types I and II only; Type III will not be considered further here. HAE episodes can manifest in a single anatomical site or can affect multiple sites simultaneously. Attacks can be painful, cause social/educational/work disability and dysfunction, and can have serious clinical sequelae, including life-threatening events, depending on the site(s) of an attack.[5] In addition to physical symptoms, HAE patients can experience negative impacts on their mental and emotional wellbeing due to anxiety caused by the fear of attack or death. HAE patients can also be self-conscious of the disfiguring symptoms of HAE attacks, causing reluctance to enter public spaces and decreasing patients' ability to perform everyday activities and other aspects of life quality. The average frequency of attacks for patients in a UK study of the timing of icatibant administration in clinical practice was over 1 attack per month (13.5 attacks per year) with a median attack duration of 48.0 hours in untreated patients.[6] HAE attacks impact on patient and caregiver school and work absenteeism, loss in productivity, and can limit educational and employment attainment. [7, 8]

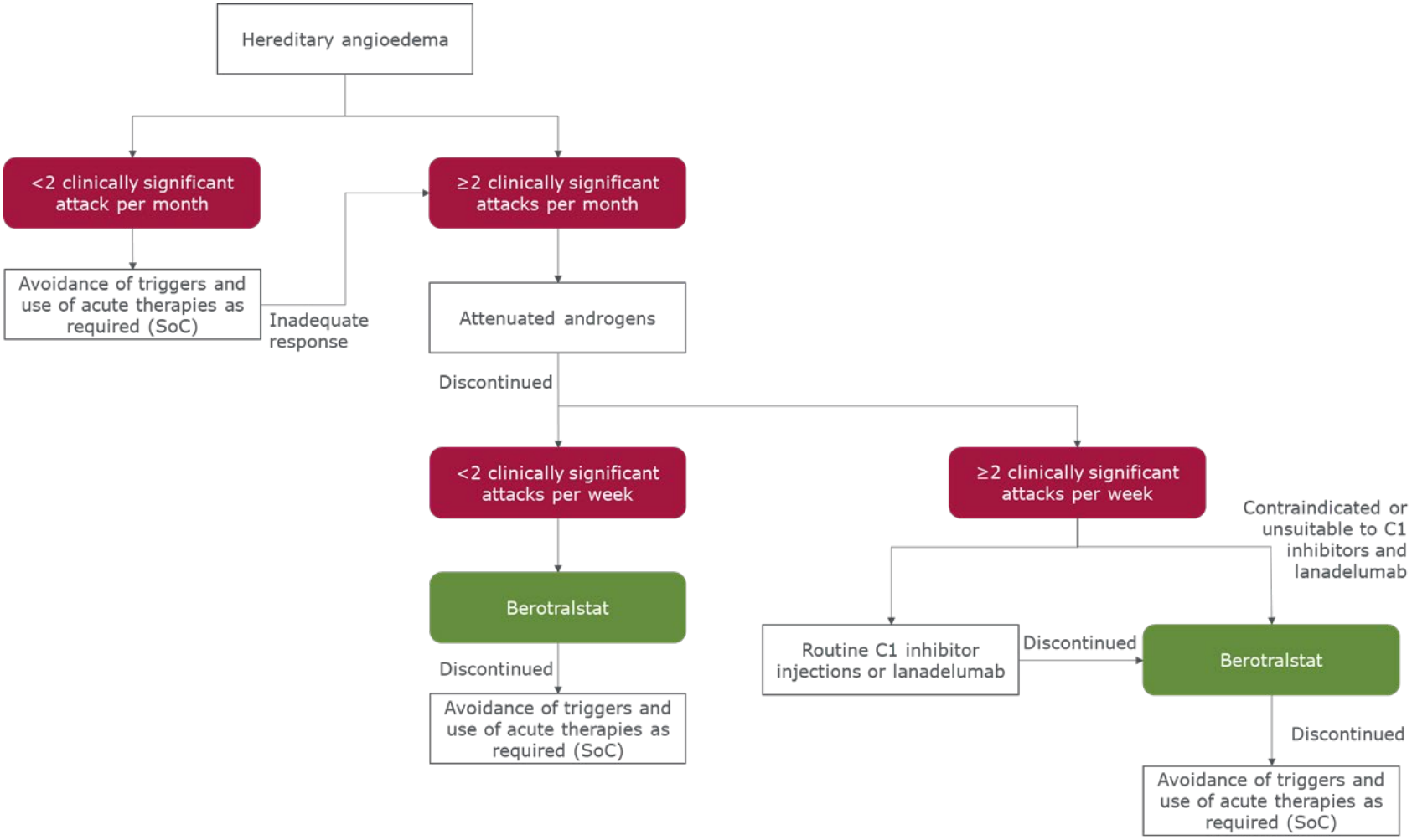
Medical attention is often required during HAE attack episodes and as part of long-term disease monitoring. Treatment options for managing HAE vary from patient to patient, reflective of the clinical heterogeneity of the condition, but generally comprise a) avoidance or treatment of known attack-precipitating factors, b) acute therapies used at the onset of, or during, an attack, c) short-term prophylaxis or d) long-term prophylaxis. There is a current lack of licensed, widely effective, safe, orally-active, long-term prophylactic treatments for HAE in the UK and worldwide. Attenuated androgens and antifibrinolytics are the only oral treatment options available for routine long-term prophylaxis in the UK;[9] however, safety/efficacy concerns with long-term use (unlicensed) of androgens mean they are often poorly tolerated or discontinued, and efficacy concerns over the use of antifibrinolytics, such as tranexamic acid, have led to a decline in consensus recommendation of their common usage.[9-11] Routine prophylaxis with injections of C1-esterase inhibitors (C1-INHs) and lanadelumab is reserved for a restricted population of patients who have a high attack frequency (≥2 attacks per week) and who are unable to tolerate oral prophylaxis, or for whom oral prophylaxis is ineffective.[1, 12, 13] Routine treatments with intravenous or subcutaneous injections may also uncommonly be unsuitable for individuals due to issues variously with venous access, venous exhaustion, technical administration challenges, risk of infection, phobia of needles, or injection site reactions such as pain and inflammation.

Standard of care for those patients in whom currently available options for long-term prophylaxis is ineffective, contraindicated or declined is avoidance of stimuli associated with triggering attacks and the administration of acute therapies when attacks occur.[9]

The company states that there is, therefore, an unmet need for effective, well-tolerated oral prophylactic treatment in HAE type I or II patients who experience ≥2 attacks per month and are unsuitable or refractory to attenuated androgens, and HAE type I or II patients who experience ≥2 attacks per week who are unsuitable for regular injectable prophylaxis with C1-INHs or lanadelumab.

The intended place of berotralstat in the current treatment pathway is shown in Figure 1, Document B of the CS and is reproduced by the ERG below as Figure x.

Figure 1: HAE treatment pathway flowchart



2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of how the company's economic modelling adheres to the NICE reference case is provided in Chapter 3. The ERG agrees that there are no issues regarding equality.

Table 3 Summary of the company's decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG's comments
Population	People aged 12 years and older with hereditary angioedema	Patients aged 12 years and older with HAE who meet the following criteria: • HAE type I or II patients who experience two or more attacks per month who are unsuitable for or refractory to androgens • HAE type I or II patients who experience two or more attacks per week and are unsuitable for regular injectable prophylaxis with C1-INHs and lanadelumab.	This population has been identified by UK clinical experts via a Delphi panel as those patients that have the greatest unmet need.[14] Patients within this population have no access to safe or effective long-term preventative therapy, instead being forced to rely on a strategy of trigger avoidance to avoid attacks, and acute treatment upon attack onset to mitigate symptoms.	The CS addresses a narrower population than that specified in the NICE final scope and focuses on • HAE type I or II patients who experience two or more attacks per month who are unsuitable for or refractory to androgens • HAE type I or II patients who experience two or more attacks per week and are unsuitable for regular injectable prophylaxis with C1-INHs and lanadelumab The ERG clinical expert is of the opinion that population addressed in the CS is appropriate for this appraisal.
Intervention	BCX7353	Berotralstat	Berotralstat is the generic name for BCX7353	The intervention described in the CS matches that described in the NICE final scope.

				The anticipated indication for berotralstat is for the routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older. The mechanism of action of berotralstat is a small-molecule inhibitor of plasma kallikrein for the prevention of attacks in HAE. Plasma kallikrein is a precursor of bradykinin. By inhibiting plasma kallikrein, berotralstat reduces the amount of bradykinin in HAE patients, thus preventing angioedema attacks.(15) Berotralstat is an oral therapy. The recommended dose is 150 mg taken once daily at approximately the same time each day with or without food. On 27 June 2018, orphan designation (EU/3/18/2028) was granted by the European Commission to BioCryst UK Ltd, United Kingdom, for berotralstat for the treatment of hereditary angioedema.(16) An application is under evaluation by the Committee for Medicinal Products

				for Human Use (CHMP) for berotralstat as a new human medicine with approval expected in Q2 2021.[17, 18] The Medicines & Healthcare products Regulatory Agency (MHRA) granted berotralstat Promising Innovative Medicine (PIM) status on 18 May 2018 and Early Access to Medicines Scheme (EAMS) status on 30th October 2020.[19]
Comparator(s)	Established clinical management for preventing acute attacks of hereditary angioedema without BCX7353 including but not limited to: • C1-INHs, attenuated androgens and anti-fibrinolytics • Lanadelumab for people eligible for C1-esterase inhibitor treatment in line with NHS England's	Standard of care (use of on demand therapy)	The positioning of berotralstat addresses the patients with the greatest unmet need, and as such it is considered that these comparators are no longer relevant. Rationale is as follows: • Attenuated androgens are unlicensed for the treatment of HAE patients and are used off label as a prophylactic treatment for the prevention of acute attacks.	The CS addresses a narrower selection of comparators than that specified in the NICE final scope. The description of the current UK treatment pathway in the CS positions berotralstat as indicated for • HAE type I or II patients who experience two or more attacks per month who are unsuitable for or refractory to androgens • HAE type I or II patients who experience two or more attacks per week and are unsuitable for regular injectable prophylaxis with C1-INHs and lanadelumab

	commissioning policy		Long-term androgen use is often discontinued due to undesired side effects or lack of efficacy.[10] The proposed positioning of berotralstat considered that patients will have already been advised against or discontinued androgen use prior to recommendation for berotralstat. As such, androgens are not direct comparators to berotralstat in the UK clinical setting. • Patients are eligible for routine C1-INHs or lanadelumab if they are	The ERG clinical expert agrees with the company's description of the current UK clinical management options and prescribing patterns. The ERG, therefore, agrees that standard care (use of on demand therapy) is the appropriate comparator for this appraisal.

			experiencing two or more clinically significant attacks per week despite oral prophylactic therapy. The eligibility criteria heavily restricts the number patients that can receive these treatments leaving the vast majority of patients no access to approved prophylactic therapy. Additionally, many patients are unsuitable for repeated injectable therapies due to difficulties locating a vein or anxiety over needles. Berotralstat aims to provide a	

			treatment option for these patients who currently have no available long-term prophylactic therapy, therefore it is not considered that C1-INHs and lanadelumab are direct comparators in the UK clinical setting. Anti-fibrinolytics such as tranexamic acid are not indicated as long-term prophylactic therapies for patients with HAE.[20] They are instead indicated to be used as a short-term treatments to be used pre-emptively before exposure to known triggers. There are also substantial efficacy concerns over the use of tranexamic acid in	

			which many studies report no significant improvement associated with the use of tranexamic acid in HAE patients.[11] As anti-fibrinolytics are only recommended for a separate indication they are not considered comparators to berotralstat.	
Outcomes	The outcome measures to be considered include: • frequency of angioedema attacks • severity of angioedema attacks • need for acute treatment • mortality • adverse effects of treatment health-related quality of life.	The following outcome measure is not included: • Severity of angioedema attacks Additional outcome measures considered include: • Location of attack (specifically differentiating between Laryngeal, Abdominal and Limb/Peripheral attacks) Duration of attacks	The severity of attack outcomes in the APeX-2 trial were self-diagnosed and patient-reported. The subjective nature of this method of data collection introduces individual level biases, reducing the validity of the data. To mitigate the influence of this bias, BioCryst propose the use of more objective measures in an attempt to convey resource use and effect on quality of life associated with attacks.	The CS addresses a narrower selection of outcomes than that specified in the NICE final scope. The rationale given in the CS for omitting severity of angioedema attacks is that this outcome was self-diagnosed and patient-reported in the APeX-2 trial and that this could introduce bias due to the subjective nature of this type of data reporting. The CS includes additional outcomes not considered in the NICE final scope. These are location of attack and duration of attack. The ERG clinical expert's opinion is that robustly defining severity of attack can be difficult as this is

			It is considered that both attack location and attack duration provide important information on both resource use and quality of life implications associated with an attack. Patients can undergo different treatment strategies dependent on attack location, while duration of attack can be used to inform the length of hospitalisation, time to apply utility decrements and the scale of loss of productivity.	highly influenced by individually subjective responses to the circumstance and physical location of attack, duration of attack, previous experiences of attacks, anxiety and experienced functional deficit. This is unpredictable and difficult to control for; therefore, the ERG agrees with the company's choice of outcomes for this appraisal.
Perspective for outcomes	The perspective on outcomes should be all direct health effects, whether for patients or other people.	The perspective for all health outcomes considers all direct health effects to patients and, where appropriate, caregivers.	This aligns with the reference case.	ERG agrees, but would value further justification for inclusion of carer utilities and the approach/assumptions used.
Perspective for costs	The perspective adopted on costs should be that of the NHS and personal and social services.	The perspective for costs in the economic analysis is for the NHS and PSS.	This aligns with the reference case.	ERG agrees
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently	A lifetime time horizon has been applied in the economic analysis.	As HAE is a lifelong condition it is appropriate to model the cost-effectiveness	ERG agrees

	long to reflect all important differences in costs or outcomes between the technologies being compared.		analysis over the lifetime of the patient. This aligns with the reference case.	
Synthesis of evidence on health effects	The Institute prefers RCTs directly comparing the intervention with 1 or more relevant comparators and these should be presented in the reference-case analysis if available.	Within the cost-effectiveness analysis all clinical data representing health effects is informed by the RCT APeX-2 which directly compares the intervention against the comparator of interest.	This aligns with the reference case.	The APeX-2 trial provides the relevant comparison given the company's proposed positioning.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The health effects within the economic analysis are expressed in QALYs. The utility values representing the relative QoL of the patients within the analysis are informed by disease specific EQ-5D data reported in Nordenfelt et al. (2014).[21]	The EQ-5D data measurements taken in the APeX-2 trial very rarely coincided with attack episodes. As a result, the EQ-5D date obtained from the APeX-2 trial is not representative of the true QoL associated with HAE. For this reason, EQ-5D data in published literature was used to represent the QoL measures associated with HAE within the cost	The ERG does not believe that the company have adequately justified discarding the EQ-5D data from the trial in favour of data from the published literature. Based on the information provided, the ERG believe it may be possible to inform the average disutility of an attack using the EQ-5D data from the trial. This approach should at least have been fully explored in the submission.

			effectiveness analysis. This aligns with the reference case and previous appraisals in HAE.[22]	
Source of data for measurement of health-related quality of life	Reported directly by patients/or carers.	The EQ-5D data presented in Nordenfelt et al. (2014) was reported directly by patients.[21] The caregiver disutilities were informed by the general population in the form of a vignette study.	The vignette study followed a TTO methodology specifically designed to elicit utility values which represent caregiver burden in absence of any EQ-5D data reported in the literature.	ERG agrees the measurement of quality of life for patients was directly reported by patients. However, quality of life impact of attacks on carers were not reported directly by carers. Rather, vignettes were used to describe quality of life impact.
Source of preference data for valuation of changes in health-related quality of life	From a representative sample of the UK population.	The changes in HRQoL is primarily informed by the difference in QoL whilst attack free compared to during an attack. EQ-5D data for both attack free and attack periods are presented in Nordenfelt et al. (2014).[21] Caregiver HRQoL data was informed by a sample of participants representative of the UK population.	Nordenfelt et al. (2014) presents the data observed in a Swedish population.[21] It is assumed QoL measures for Swedish HAE patients will be similar to those expected in the UK population. This aligns with previous appraisals in HAE.[22]	Partially met.
Evidence on resource use and costs	Costs should relate to resources that are under the control of the NHS	Resource use was informed by the mean rates observed by UK	This aligns with the reference case.	ERG agrees

	and personal and social services. These resources should be valued using the prices relevant to the NHS and personal and social services.	clinicians in clinical practice. All cost inputs were sourced from UK national data bases such as the BNF, NHS reference costs and PSSRU.		
Discounting	The same annual discount rate should be used for both costs and benefits (currently 3.5%).	An annual discount rate of 3.5% is applied to both cost and health benefits.	This aligns with the reference case.	ERG agrees

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The ERG appraisal of the company's systematic review methods is summarised in Table 4.

Table 4 ERG's appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources searched were Embase, Medline (via Embase interface), and CENTRAL for primary research. DARE, ScHARRHUD, EuroQol, and HTA organisations were searched for evidence syntheses. Relevant conference proceedings and the web sites of health organisations were also searched. Details are provided in Appendix D of the CS.
Were eligibility criteria consistent with the decision problem	Yes	See Appendix D, Section D.4, Table 1 of the CS.

outlined in the NICE final scope?		
Was study selection conducted by two or more reviewers independently?	Yes	See Appendix D, Section D.6 of the CS. Two independent reviewers assessed the relevance of studies for inclusion.
Was data extraction conducted by two or more reviewers independently?	Yes	See Appendix D, Section D.7 of the CS. Data were extracted by one reviewer and checked for accuracy by a second reviewer.
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	See Appendix D, Section D.7 of the CS and response to the ERG clarification letter. The risk of bias tools used were Cochrane Risk of Bias Tool for RCTs and the Newcastle-Ottawa Scale for non-RCTs.
Was risk of bias assessment conducted by two or more reviewers independently?	Yes	See response to ERG clarification letter. The risk of bias was initially assessed by one reviewer and validated by a second reviewer. Following the response to the ERG question, to meet the requirement of a double independent assessment, an additional posterior assessment was performed independently by a second reviewer.
Was identified evidence synthesised using appropriate methods?	Yes	Results of APeX-2 trial. No meta-analysis or indirect treatment comparisons.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for

Review and Dissemination (CRD) criteria. The results are presented in Table 5.

Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

Based on a systematic literature review, the company identified one randomised controlled trial (RCT) evaluating the clinical efficacy and safety of berotralstat for the prevention of HAE attacks: the APeX-2 trial. The key evidence in the CS for the efficacy and safety of berotralstat for the prevention of attacks in patients with HAE is, therefore, based on the APeX-2 RCT.[23]

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

Details of the key clinical effectiveness evidence are provided in Table 3, Document B of the CS and this is reproduced by the ERG as Table 6 below.

Table 6 Clinical effectiveness evidence: the APeX-2 trial

Study	APeX-2 (NCT03485911)
Study design	Phase III randomised, double-blind, placebo-controlled multi-centre, three-part trial
Population	Adults and adolescents (≥12 years of age) with Type 1 or Type 2 HAE
Intervention(s)	110 mg berotralstat (N=41) or 150mg berotralstat (N=40) administered orally once daily for 24 weeks
Comparator(s)	Placebo (N=40) administered orally once daily for 24 weeks
Indicate if trial supports application for marketing authorisation	Yes
Indicate if trial used in the economic model	Yes
Rationale for use/non-use in the model	APeX-2 provides efficacy and safety data concerning the use of berotralstat as a treatment for the prevention of HAE attacks in patients aged 12 years or older with Type 1 or 2 HAE.
Reported outcomes specified in the decision problem	• Frequency of angioedema attacks • Severity of angioedema attacks • Need for acute treatment • Mortality • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	• **Location of attack** • **Duration of attacks**

The APeX-2 trial was a Phase III randomized, double-bind, international, multicenter RCT that compared 110mg berotralstat or 150mg berotralstat with placebo in people with Type 1 or Type 2 HAE aged 12 years or older. Details of the trial methodology and inclusion and exclusion criteria are provided in Tables 4 and 5, Document B of the CS. Participants had to demonstrate ≥ 2 HAE attacks that met all qualification requirements during a prospective run-in period of 14 to 56 days from the date of screening to be eligible for trial entry. HAE attack requirements were that the attacks were unique (defined as an

attack that did not begin with 48 hours of the end of a previous attack); attacks must have been either treated, required medical attention, or been recorded as causing function impairment; attacks included symptoms of swelling and attacks were confirmed by the investigator to be HAE attacks. All patients were required to have access to approved treatments for attacks of angioedema as part of their routine medical care. Approved treatments included icatibant, plasma-derived C1-INH, ecallantide, recombinant C1-INH and cinryze (used for acute treatment of HAE attacks only). Each patient continued to use their prescribed HAE standard of care acute attack medications (SOC-Rx) to treat any attacks throughout the study. Details of disallowed concomitant medication are provided in Table 5, Document B of the CS. The ERG is satisfied that the trial inclusion and exclusion criteria and list of permitted and disallowed treatments are appropriate for the current appraisal.

The trial was conducted in three parts. In part 1 participants were randomised 1:1:1 to either 110mg berotralstat (n=41), 150 mg berotralstat (n=40), or placebo (n=40). All treatments were administered orally once daily for 24 weeks. Part 2 of the trial began at the end of week 24, participants in the two berotralstat treatment arms continued to receive the same blinded dose to which they had been randomised to in Part 1. Participants who had been randomised to the placebo arm underwent a second 1:1 randomisation to one of the two-berotralstat arms. These participants were aware that they would receive active treatment but both patients and outcome assessors were blinded to the dose strength. Part 3 of the trial began at week 48 where participants continued to receive the same phase two berotralstat treatment regimen but were unblinded to the treatment dose. The company explain that the 110mg dose of berotralstat is not clinically relevant to the current submission as this dose will not be licensed or marketed in the UK and, therefore, does not present results for this treatment dose. Whilst recognising that HAE is a rare disease, the ERG notes that the data presented in the CS are limited to a single trial of 80 patients.

Details of the baseline characteristics of the APeX-2 participants are provided in Table 6, Document B of the CS and details of the baseline AE-QoL scores are provided in Table 2 of the company's clarification letter. These data are reproduced by the ERG as Table 7. The mean participant age of HAE symptom onset was 11 years and mean age at diagnosis was 20 years. Participants were reasonably balanced between the two treatment arms in terms of their baseline AE-QoL scores and demographic details, although participants in the berotralstat arm had a higher median weight than participants in the placebo arm (82kg versus 77kg). Slightly more female participants were enrolled in the placebo arm than in the berotralstat arm (57.5% versus 67.5%), and slightly fewer placebo participants had no prior androgen use compared with berotralstat participants (35% versus 45%). The ERG' clinical expert agrees that the APeX-2 trial participants are representative of HAE patients seen in UK clinical practice in terms of the demographic characteristics and that the baseline differences are unlikely to impact on the trial results.

Table 7 Baseline characteristics of the APeX-2 trial

	Berotralstat 150mg QD	**Placebo QD**
APeX-2 (N =121)	**n=40**	**n=40**
Region		
North America	27 (67.5%)	28 (70.0%)
Europe	13 (32.5%)	12 (30.0%)
Sex, n (%)		
Male	17 (42.5%)	13 (32.5%)
Female	23 (57.5%)	27 (67.5%)
Race, n (%)		
White	38 (95.0%)	37 (92.5%)
Other	2 (5.0%)	3 (7.5%)
Age at time of consent (years)		
Mean (SD)	40.0 (13.98)	44.5 (14.12)
Adolescent (12-17 years)	[redacted]	[redacted]

	Berotralstat 150mg QD	**Placebo QD**
Adult	[redacted]	[redacted]
18-64 years	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]
Baseline investigator-confirmed attack rate[a], n (%)		
≥ 2 attacks/month	30 (75.0%)	27 (67.5%)
< 2 attacks/month	10 (25.0%)	12 (30.0%)
Baseline weight		
Mean (SD)	87.62 (20.378)	84.87 (21.351)
Baseline BMI[b,c,d], n (%)		
Underweight	0	0
Healthy weight	8 (20.0%)	12 (30.0%)
Overweight	16 (40.0%)	14 (35.0%)
Obese	16 (40.0%)	13 (32.5%)
Prior androgen use[b,e], n (%)		
Yes	22 (55.0%)	25 (62.5%)
No	18 (45.0%)	14 (35.0%)
AE-QoL total score		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]

AE-QoL, Angioedema Quality of Life

Notes: [a] The categorised baseline investigator-confirmed attack rate was defined as the total number of investigator-confirmed HAE attacks experienced in the period between screening and first dose of study drug adjusted for the length of a month (defined as 28 days) and the number of days during that period (ie, date of first dose - date of screening visit + 1). [b] Reported from an ad-hoc analysis. [c] Median weight of all patients in the ITT population of 78.96 kg. [d] Categorisation of BMI was based on CDC reported values for adults: < 18.5 kg/m2 = underweight, 18.5 - 24.9 kg/m2 = healthy weight, 25.0 - 29.9 kg/m2 = overweight, > 30 kg/m2 = obese (McDowell, Hughes et al. 2006). [e] Prior androgens were as noted on the HAE Medical and Medication History - Part 1 eCRFs. These medications include any of the following: androgens (unspecified), oxandrolone, methyl-testosterone, danazol, and stanozolol.

The primary efficacy endpoint of APeX-2 was the rate of investigator-confirmed HAE attacks during the part-1 treatment phase (day 1 to week 24). The secondary endpoints were: change from baseline in Angioedema Quality of Life Questionnaire (AE-QoL) total score at week 24 (the minimal clinically important difference [MCID) is -6); the number and proportion of days with angioedema symptoms through the 24-week treatment period; the rate of investigator-confirmed during dosing in the effective treatment period. Safety outcomes included: treatment-emergent adverse events (TEAEs); discontinuation due to TEAEs; treatment-emergent serious adverse events (SAEs); Grade 3 or Grade 4 TEAEs.

The methodological quality of APeX-2 was judged by the company to be at low risk of bias for all domains of the Cochrane risk of bias tool for assessing RCTs. The ERG agrees with the company's risk of bias judgement.

3.2.2 Primary and secondary efficacy endpoints

An overview of the APeX-2 primary and secondary efficacy endpoint data are presented in Table 8. The ERG agrees that the approach to the statistical analysis of the APeX-2 trial is appropriate.

Primary efficacy endpoint: rate of investigator-confirmed HAE attacks

Over the 24-week treatment period, berotralstat 150 mg was associated with a statistically significant reduction in the rate of investigator-confirmed HAE attacks compared to placebo (-44.2%; 95% CI: -59.5, -23.0; p<0.001). The analysis estimated attack rates per 28 days of 1.31 for patients treated with berotralstat 150 mg patients, compared with 2.35 for patients who received placebo. The berotralstat 150 mg treatment group had a mean attack rate of [redacted] attacks per month (median: [redacted] attacks per month) at baseline, [redacted] per month (median: [redacted] per month) in Month 1, and [redacted] per month (median: [redacted] per month) at the end of month 6. There was no evidence of drug tolerance developing over Part 1. The company presents the difference in mean investigator-confirmed attacks by month for each treatment arm in Figure 4, Document B of the CS, reproduced by the ERG as Figure 2 below. The reduction in mean attack rate was [redacted] over the 24 to 48 week

period. The company presents this data in Figures 6 and 7 of the CS. In patients re-randomised to berotralstat 150 mg after placebo, there was a [redacted] in investigator-confirmed HAE attacks from [redacted] at month 6 on placebo to [redacted] at month 12 on berotralstat 150 mg.

The company performed a number of sensitivity analyses on the primary efficacy endpoint. These are presented in section B.2.6.2 of the CS. These analyses demonstrated that berotralstat was associated with a statistically significant reduction in investigator-confirmed HAE attacks compared with placebo. The ERG notes that the sensitivity analyses cover a wide range of scenarios (from analysis on the per-protocol population to ITT analysis with imputation for missing data) and that their results remain consistent with the primary ITT analysis.

Figure 2: Plot of Mean Investigator-confirmed Attack Rate by Month (ITT Population)

Source: APeX-2 CSR[23]
Abbreviations: ITT, intent to treat; N, number of patients

Secondary efficacy endpoints: AE-QoL total score, number and proportion of days with angioedema symptoms through 24 weeks, rate of investigator confirmed HAE attacks during dosing in the effective treatment period

The change from baseline AE-QoL total scores indicated greater improvements in quality of life (QoL) for participants treated with berotralstat compared with placebo. The least squares mean (LSM) difference from placebo in AE-QoL total score was -4.9 (95% CI: -12.2, 2.4; p = 0.188) for the berotralstat 150 mg treatment group at 24 weeks. Improvements in the mean change in AE-QoL total score were sustained throughout parts 1 and 2 of the trial. At week 48, the mean (SD) change from baseline in AE-QoL total score was [redacted]), and 77% of patients showed improvements in AE-QoL that exceeded the MCID total score. The mean change from baseline in total AE-QoL score over time to week 48 for berotralstat is shown in Figure 8, Document B of the CS.

Berotralstat treatment was associated with fewer days of symptomatic angioedema. The mean number of days patients experienced angioedema symptoms from investigator-confirmed attacks was 19.4 and 29.2 days for the berotralstat 150 mg and placebo treatment groups, respectively.

For the rate of investigator confirmed HAE attacks during dosing in the effective treatment period, berotralstat was statistically significantly better than placebo. The reductions in attack rate relative to the placebo treatment group was 47% (95% CI: 0.39, 0.74; nominal p < 0.001) for the berotralstat 150 mg treatment group.

Table 8 Overview of the primary and secondary endpoints assessed in the APeX-2 trial

Primary Endpoint				
Investigator-confirmed attack rate[a]	**Berotralstat 150mg; N=40**			**Placebo; N=40**
	Rate per 28 days	Active vs Placebo % (95% CI)	P-value	Rate per 28 days
	1.31	-44.2% (-59.5, -23.0)	< 0.001	2.35
Secondary Endpoints				
AE-QoL total score change from baseline (ITT population)	***Berotralstat 150mg; N=[redacted]***			***Placebo; N=[redacted]***
LSM	[redacted]			[redacted]
Standard error	[redacted]			[redacted]
LSM difference from placebo	[redacted]			[redacted]
95% CI	[redacted]			[redacted]
P-Value	[redacted]			[redacted]
Number and proportion of days with angioedema symptoms through 24 weeks	***Berotralstat 150mg; N=40***			***Placebo; N=40***
Mean number of days	19.4			29.2
Investigator-confirmed attack rate	Berotralstat 150mg; N=40			Placebo; N=39
Mean (SD)	[redacted]			[redacted]
Median	[redacted]			[redacted]
Range	[redacted]			[redacted]
Negative binomial regression analysis				
Estimated rate	1.27			2.38
Attack rate ratio (relative to placebo)	0.54			
95% CI about attack rate ratio	0.39, 0.74			
P-Value	< 0.001			
Rate reduction from placebo	46.5%			

Abbreviations: AE-QoL, Angioedema Quality of Life; CI, confidence interval; ITT, intent to treat; LSM, least squares mean; N, number of patients; SD, standard deviation
Notes: [a] Investigator-confirmed attack rate was defined as (total number of investigator-confirmed HAE attacks experienced in the period between first date/time of study drug in Part 1 and the first dose date/time in Part 2 [or the last dose date/time of dose in Part 1 + 24 hours for patients who

discontinued drug in Part 1]) × 28/(date of first dose in Part 2 [or date of last dose in Part 1] - date of first dose in Part 1 + 1).
Source: APeX-2 CSR[23]

Exploratory endpoints

The company presents a number of exploratory endpoints from APeX-2 in section B.2.6.4 of the CS. These include: responder analysis, use of HAE standard of care acute attack medication (SOC-Rx), location and duration of attack, and EQ-5D-5L scores.

At 24 weeks, a higher percentage of berotralstat patients experienced a ≥50% and ≥70% reduction in attack rate relative to baseline compared with placebo patients ([redacted]% versus 25% and 50% versus 15% respectively). Berotralstat was associated with a reduction in HAE SOC-Rx by 49% ([redacted]) compared with placebo. Berotralstat reduced peripheral-only attacks by [redacted] ([redacted]). An ad-hoc analysis of laryngeal attacks showed that treatment with berotralstat reduced laryngeal attacks by [redacted] ([redacted]) compared with placebo. Berotralstat was also associated with [redacted] of HAE attack compared with placebo ([redacted] hours versus [redacted]). Attack durations by location are provided in Table 13, Document B of the CS. For all locations (abdominal-only, peripheral-only, and mixed-location) the duration of attack is shorter in the berotralstat treatment arm compared with placebo. Participants who received [redacted].

3.2.3 Subgroup analysis

Prespecified subgroup analyses of the primary efficacy endpoint were performed for [redacted] In general, the subgroup analyses support the effectiveness of berotralstat in reducing the rate of HAE attacks; however, the

ERG notes that analyses for some of the pre-specified subgroups relies on a very small number of participants and, therefore, should be treated with caution.

3.2.4 Adverse reactions

The company presents details of the adverse reaction data for APeX-2 in section B.2.10, Document B of the CS. For most participants in the two arms of APeX-2 exposure to berotralstat 150 mg was between >12 to ≤ 24 weeks. While slightly more berotralstat participants experienced a drug-related TEAE than placebo participants (37.5% versus 33.3%), [redacted] berotralstat participants experienced any Grade 3 or 4 TEAE than placebo participants ([redacted] versus [redacted]) over the trial period. One patient in each treatment arm discontinued the study drug due to a TEAE. All TEAEs are described as mild to moderate. A summary of the most frequently reported TEAEs is presented in Table 18, Document B of the CS, and is reproduced by the ERG as Table 9 below.

No treatment-emergent SAEs were considered related to study treatment. There were no deaths in either treatment arm during the study.

Table 9 Most Frequently Reported (≥5% the Total Number of Subjects) TEAEs by Preferred Term (Safety Population)

TEAE (preferred term)	Berotralstat150mg; n=40 n (%) [events]	Placebo; n= 39 n (%) [events]
Nasopharyngitis	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Abdominal discomfort	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Flatulence	[redacted]	[redacted]
Gastroesophageal reflux disease	[redacted]	[redacted]

Oropharyngeal pain	[redacted]	[redacted]

Source: APeX-2 CSR[23]
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; n, number of patients who experienced the event; TEAE, treatment-emergent adverse event.

3.2.5 Meta-analyses

No meta-analyses were carried out by the company due to the lack of suitable evidence.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company states that, because APeX-2 provides a direct comparison between berotralstat and placebo, an indirect treatment comparison is not considered necessary to provide additional evidence to support this submission. While the ERG agrees that an indirect treatment comparison is not possible due to the lack of available evidence, has some concern about the current limited clinical evidence available for berotralstat (one trial of small sample size).

3.4 Critique of the indirect comparison and/or multiple treatment comparison

No indirect and mixed treatment comparisons were carried out by the company.

3.5 Additional work on clinical effectiveness undertaken by the ERG

None

3.6 Conclusions of the clinical effectiveness section

The company's decision problem is appropriate for addressing the final scope issued by NICE in relation to this appraisal. Overall, the ERG consider the methods used to conduct the systematic review of clinical effectiveness evidence to be in line with current methodological standards.

The main source of clinical evidence submitted by the company consists of a phase III, double blind RCT, APeX-2. Results of the APeX-2 trial indicate that treatment with berotralstat for 24 weeks has clinical benefit over placebo and that this benefit are sustained over time (up to 48 weeks); however, the ERG notes that this clinical

results are based on a single trial with a sample size of only 80 patients and limited long-term follow-up data.

While participants who received berotralstat were more likely to experience a drug-related TEAE than placebo participants over the trial period, these were reported to be mild to moderate and no unexpected adverse events were observed. The ERG has no concerns about the safety profile of berotralstat based on the results of the APeX-2 trial, but notes the lack of long-term safety data.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

As detailed in appendix G of their submission, the company conducted a systematic literature review to identify cost-effectiveness, health-related quality-of-life (HRQoL), and cost and resource use publications conducted in hereditary angioedema (HAE). This is described as an update to a previous SLR conducted by the company, but with broader scope to include carer disutility and indirect costs due to lost productivity. The original SLR identified studies to 10th October 2019. The update identified studies published since 10th October 2019, up to 10th September 2010, and further studies published prior to 10th October 2019 which met the modified search/selection criteria.

The selection criteria were sufficiently broad to capture cost-effectiveness studies (including cost-utility analysis) of any intervention for HAE types 1 and 2. The searches covered an appropriate range of databases, HTA agency websites, and conference proceedings, and used relevant search terms.

Four cost-effectiveness studies were identified: 1) a US modelling study comparing lanadelumab, Haegarda, and Cinryze prophylaxis to no prophylaxis in type 1 and 2 HAE;[24] 2) a US modelling study comparing prophylaxis with C1-INH subcutaneous (SC) to C1-INH intravenous (IV) over a one-year time horizon in terms of costs and attacks avoided;[25] 3) a US study assessing cost-effectiveness of alternative on-demand treatments for acute attacks;[26] and 4) an Irish HTA agency (National Centre for Pharmacoeconomics (NCPE)) appraisal assessing the cost-effectiveness of lanadelumab prophylaxis versus C1-INH prophylaxis.[27]

The company do not draw any firm conclusions regarding cost-effectiveness form their literature review given the lack of applicability to the current decision problem. However, they note several general limitations with respect to cost-effectiveness modelling in HAE, the main one being limited data available given the rarity of the condition.

The ERG is satisfied with the conduct of the company's review of cost-effectiveness studies. Of the four studies identified, only the one model compared prophylaxis with no prophylaxis, and is perhaps most structurally relevant to the decision problem in the current TA. This study reported QALY gains versus no prophylaxis that ranged from 0.74 (C1-INH Cinryze) to 1.19 (lanadelumab). Perhaps greater discussion of this Institute for Clinical and Economic Review (ICER) study could have helped to justify and cross-validate the company's own model structure and assumptions. It should be noted, however, that the company have drawn more detailed comparisons between their own model and the model used in the NICE appraisal of lanadelumab for prevention of HAE attacks (TA), although for some reason the latter was not reported in the SLR of cost-effectiveness studies.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 10: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	ERG agrees, but would value further justification for inclusion of carer utilities and the approach/assumptions used to do so.
Perspective on costs	NHS and PSS	Aligns with reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Aligns with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Aligns with reference case
Synthesis of evidence on health effects	Based on systematic review	A systematic review was conducted, but all the clinical effectiveness evidence comes from the single trial (APeX-2)

Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes, QALYs used, although carer QALY losses based on values elicited for vignettes. The ERG does not believe that the company have adequately justified discarding the EQ-5D data from the trial in favour of data from the published literature
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The measurement of quality of life for patients was directly reported by patients. However, quality of life impact of attacks on carers was described using vignettes.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Aligns with the reference case. Although the source of patient EQ-5D data was a from a Swedish study, the UK cross walk value set was used to assign values.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Aligns with the reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Aligns with the reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Aligns with the reference case
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company developed a simple two-state Markov cohort model, the health states being “Alive” and “Dead”. Within the alive state, the cohort is subdivided into two

sub-states: those currently experiencing an HAE attack and those currently attack free. The time spent in each of these sub-states is determined by treatment specific attack rates taken from the APeX-2 trial. The model in fact uses percentage reductions from baseline attack rates in the berotralstat and placebo arms of APeX-2, applied to the baseline attack rates specified in the model. Those in the attack sub-state incur the costs of acute attack and lower QALYs compared to those in the attack free state. The model uses a 28 day cycle.

Within the model, a treatment continuation rule is applied, whereby only patients who achieve a 50% or greater reduction in attack rate by 3 months continue treatment with berotralstat.

The ERG is satisfied that the model structure is generally appropriate for addressing the decision problem, and similar to that used in the previous NICE appraisal of lanadelumab for preventing recurrent attacks of hereditary angioedema (TA606).[22] *However, the ERG has some concerns regarding the parameterisation of the model, as outlined in the following sections.*

4.2.3 Population

The company have focussed their submission on a sub-group of the technology's anticipated licenced indication (Company submission, document A, A.4) - "those patients aged 12 years and older that require routine prevention of recurrent attacks of hereditary angioedema who are appropriate for prophylactic treatment and are unsuitable or refractory to androgens. The proposed position in the treatment pathway is as follows:

- HAE type I or II patients who experience two or more attacks per month and are unsuitable or refractory to androgens;
- HAE type I or II patients who experience two or more attacks per week and are unsuitable for regular injectable prophylaxis with C1-INHs and lanadelumab.

T*he ERG agrees that the positioning addresses the area of greatest unmet need in the NHS in England; i.e. those who would benefit from, but currently do not have*

access to, prophylactic treatment because, either: a) they do not meet NHS England's commissioning criteria for access to C1-inhibitors or lanadelumab,[13, 22] or b) they meet the criteria but have been deemed unsuitable for regular prophylaxis with C1-inhibitors or lanadelumab. The ERGs clinical advisor noted that with good patient selection (and at the current UK level of experience of these treatments, especially lanadelumab and subcutaneous C1-inhibitors), the latter subgroup is likely to be small as unsuitability due to potential treatment-excluding factors, in isolation or in combination (adverse reactions, training or technical administration difficulties, concurrent medications, other diseases or non-clinical issues etc.) is liable to be relatively uncommon.

4.2.4 Interventions and comparators

Given the company's positioning, the comparator in the economic model is treatment on demand for acute attacks, informed by the placebo arm of APeX-2. The intervention is berotralstat 150mg (once daily), the anticipated licensed dose in the UK.

The ERG accepts that the choice of comparator is in line with the company's positioning.

4.2.5 Perspective, time horizon and discounting

The perspective of the modelling is line with the NICE reference case with respect to costs and health outcomes. In terms of health outcomes, the company include health benefits accruing to patients and carers. A 56-year time horizon is adopted, which is in line with a lifetime horizon based on the average age of the modelled cohort (44 years). The average age reflects the baseline age of the subgroup of APeX-2 meeting the company's proposed positioning.

4.2.6 Treatment effectiveness and extrapolation

Data used to inform the model inputs

The model is driven by percentage reductions from baseline attack rates. The percentage reductions for berotralstat and SoC (treatment on demand) are based on the observed percentage reductions in the berotralstat 150mg and the placebo arms of APeX-2, respectively. However, in line with the company's proposed positioning,

the originally submitted model only utilised data for those in APeX-2 who experienced an attack rate of ≥ 2 per month during the screening period (14-56 days) prior to randomisation, and who had previously used androgens at baseline. The former criterion was a minimisation factor in the randomisation process (<2, ≥ 2 per month), but the latter was not.

Whilst the ERG acknowledge that the company have focussed on patients in APeX-2 that would be eligible for treatment in accordance with their proposed positioning in the NHS in England, it does result in the model inputs being based on data from a small number of patients (n=35, 17 berotralstat patients and 18 SoC patients). Furthermore, since the model applies a treatment continuation rule in which only those who experience a 50% or greater reduction in attack rate by 3 months continue on berotralstat, the number of patients informing the longer-term percentage reduction in attack rates for berotralstat is further reduced (n=[redacted]). This leads to a substantial degree of uncertainty around the percentage reductions applied, to which the model results are sensitive.

Since percentage reductions from baseline are the key efficacy input in the model, and the company subgroup analysis did not provide evidence to suggest that attack rate at baseline or previous androgen use are significant relative effect modifiers, the ERG requested a scenario analysis in which the model inputs were based on the whole ITT population of APeX-2 but applied to a baseline attack rate in line with the company's propose positioning (Clarification letter, B22). This would assume that the percentage reductions from baseline and other attack specific inputs (durations, locations, acute treatment distributions and resource use etc) are generalisable across the subgroups. The benefit of this approach is that it provides more data to inform the model inputs and retains the randomised structure of the data.

In response to this request, the company argued that such an approach is not clinically appropriate, but their arguments focus on reiterating their claim that the subgroup of patients with ≥2 attacks at baseline and prior androgen use was selected to be most representative of those patients who will be treated with berotralstat in UK clinical practice. They do not offer clear arguments as to why the

percentage reductions in attack rates from baseline in the ITT population should not be generalisable to those who meet the criteria for their proposed positioning.

Nevertheless, the company did provide additional scenarios in which they based the model inputs on all patients who experienced ≥2 attacks per month at baseline (including those with no previous experience of androgens). The ERG believes this to be a relevant scenario analysis, as based on the company's subgroup analysis and the ERG's clinical expert advice, it could not identify a reason why previous androgen use at baseline should modify the relative response to berotralstat which has a different mechanism of action to attenuated androgens. Further, the ERGs clinical expert noted that patients may discontinue androgens due to intolerable side effects rather than lack of efficacy, suggesting that those with prior experience of androgens do not necessarily represent an intrinsically harder to treat population. It can be noted that the additional scenarios provided, based on the larger subgroup with ≥2 attacks per month at baseline, result in substantial increases in the ICER for berotralstat.

Extrapolation of percentage reductions in attacks beyond the observed follow-up period of the trial

To inform monthly percentage reductions in attack rates from baseline to 12 months for berotralstat, and to 6 months for SoC, the company used observed data for the subgroup of APeX-2 meeting the criteria of the proposed positioning (n=35). Beyond this they used the last observed percentage reduction carried forward over the remaining time horizon of the model.

As mentioned, the percentage reductions for berotralstat were based on all those meeting the criteria of the positioning up to 3 months (n=17), but beyond this time point they were based on the responders (n=[redacted]).

The ERG has several concerns regarding the company's methodological approach:

a. *It relies on treatment arm specific baseline attack rates, rather than adjusting for these and setting them equal between the arms.*

b. The percentage reductions for responders (n=[redacted]) were calculated from the average baseline attack rate of the wider subgroup (n=17), rather than the baseline attack rate of responders.
c. Applying the last observation carried forward fails to recognise the observed variation in monthly attack rates compared to baseline and may by chance (particularly given the small numbers) exaggerate the expected difference in the attack rate between the berotralstat and SoC arms over the duration of the model. This is because the last observation (at 12 months) for berotralstat responders happened to be one of the lower observed monthly rates, and the last observation on the placebo group was the highest rate observed over 6 months.

To address these potential biases in the context of the company's model structure, the ERG would have preferred an analysis that:

a. set the baseline attack rates equal between the arms;
b. calculated and applied mean percentage reductions for responders relative to the baseline attack rate of the responders (n=[redacted]), not the wider subgroup (n=17).
c. Carried the average monthly attack rate forwards rather than the last observation; i.e. averaging across months 4-12 for berotralstat responders, and months 1-6 for SoC patients.

This approach attempts to adjust for between group differences and within group variation (between berotralstat non-responders and responders) in baseline attack frequency, and could provide a more generalisable approach for assessing cost-effectiveness by different baseline attack rates (equalised between arms) - assuming that percentage reductions from baseline are not significantly modified by the absolute baseline attack rate.

The ERG asked for the company to conduct additional scenarios incorporating each of these changes in the clarification letter. The company provided these, but also provided a defence of their last observation carried forward (see Company response the question B4 of the clarification letter). This hinged on the company's assertion that patients in the placebo arm of APeX-2 initially experienced a reduction in attack rate (months 1-5) due to a placebo effect, which then wore off by month 6 (Figure 3).

Since patients would not receive a placebo drug in routine practice, they claim it is inappropriate to incorporate the reduction observed through months 1-5 in the estimated attack rate carried forward in the SoC arm of the model. However, they did not provide any additional evidence to support this assertion. Whilst the company did provide a scenario that applied the average, they prefer the last observation carried forward. They also suggested another scenario that holds the SoC attack rate constant at baseline.

Figure 3: Reduction in attack rate from baseline for Months 0-6 for patients with ≥2 attacks per month and prior androgen use at baseline treated with SoC in APeX-2 (reproduced from Figure 1 of the company's response to the clarification letter)

The ERG believes that the average monthly attack rates do represent an appropriate scenario to consider given the monthly variation in mean attack rates observed in both arms of APeX-2. The ERG's clinical expert also advised that within-individual attack frequency can vary from month to month. It is plausible that some of those in the subgroup of APeX-2 experiencing ≥ 2 attacks per month at baseline were recruited during a month when they were experiencing a spike in their attack rate, in which case the observed dip in the placebo arm attack rate (months 1-5) may represent natural variation. However, the ERG believes the company's alternative scenario of carrying forward the baseline attack rate should also be considered -

assuming that the baseline measure is an accurate reflection of the average expected attack rate over time.

With respect to extrapolation of the attack rate in berotralstat responders, the ERG does not see convincing data to favour the last observation over the average observed over months 4-12. Afterall, based on consultation with clinical experts, the company suggest that 3 months after treatment initiation is a suitable time to determine whether berotralstat treatment has been successful or not. Furthermore, looking at the observed monthly attack rates for responders (n=[redacted]), there is no obvious trend towards efficacy increasing further with longer follow-up beyond month 3 (Figure 4).

Figure 4: Reduction in attack rate from baseline for Months 1-12 for patients with ≥2 attacks per month and prior androgen use who experience a ≥50% reduction in attack frequency by 3 months

A further concern of the ERG regarding the company's modelling was the characterisation of uncertainty around the estimated ICER. Whilst basing the key efficacy inputs (percentage reductions in attack rates) on small numbers of patients, the probabilistic sensitivity analysis presented in the company's submission applied 10% of the mean percentage reductions to represent the standard errors for these important inputs. This will likely underestimate the uncertainty surrounding the cost-effectiveness estimates.

The company provided a revised PSA in their response to the clarification letter in which they incorporated the actual standard errors based on the data (see company

response to question B16 of the clarification letter). The company noted that "the use of the standard error estimates obtained from the trial introduces levels of variation that are too extreme for any true impact of uncertainty to be identified." They note that "including these standard errors in the economic model leads to a much larger degree of variation in the estimates for the percentage reduction in attack rates each cycle", and that this "leads to a skewness which results in extreme values that reduce the relative efficacy of berotralstat being observed more frequently than extreme values that improve the relative efficacy of berotralstat compared against SoC."

The ERG believe that the company response partly supports its concern that the original PSA downplayed the decision uncertainty given the data used. However, the ERG agrees that the alternative approach, as implemented, may bias the ICER as the company suggest. This may be due to small numbers being used to inform independent distributions in each arm of the model; i.e. ignoring likely correlation between the attack rate distributions applied in each arm.

Considering this further, the uncertainty might have been better represented with a model using relative treatment effects for berotralstat and berotralstat responders versus placebo. The attack rates for those on berotralstat could then have been modelled relative to the attack rates in the SoC arm. Such an approach was applied and accepted in the appraisal of lanadelumab, although without the complication of a continuation rule being applied. Using the output of a regression, adjusting for baseline attack rate, the treatment effect distributions could have been correlated with the distribution for the constant term (representing the adjusted mean baseline attack rate in the placebo (SoC) arm).

4.2.7 Health related quality of life

In the base case analysis, health-related quality of life (HRQoL) data are applied in the model in three ways:

- A 'baseline' attack-free utility value to capture patients' QoL between HAE attacks. All decrements are deducted from this value
- HAE attack disutilities to capture the QoL loss during an attack

- Caregiver attack disutilities applied to account for QoL loss due to the anxiety impact on caregivers of patients with HAE

EQ-5D-5L data collected in the trial

EQ-5D-5L visual analogue scale (VAS) and index scores were collected in the APeX-2 trial at baseline and weeks 4, 8, 12, and 24. Figure 9 in the CS (reproduced below) summarised the EQ-5D-5L VAS and Index scores for all patients in APeX-2 and based on these data the company concluded that [redacted] See figure 5 below.

Figure *5*: EQ-5D-5L VAS and Index results (reproduced from CS, Figure 9)

The company highlights a number of limitations with the EQ-5D-5L data meaning they consider it unsuitable for use in the economic model. Firstly, it is noted that as HAE attacks are unpredictable, it would have been unlikely for these attacks to coincide with the five EQ-5D-5L data collection time points in the trial. Secondly, patients were asked to report their HRQoL based on recall which was noted as being less robust. The insensitivity of the generic EQ-5D-5L measure was noted as being a further limitation of its use in HAE, although no further evidence is provided to support this assertion. Due to these limitations, the EQ-5D-5L data were not used in the economic model.

The use of EQ-5D in APeX-2 to measure and value the QoL of patients eligible to receive berotralstat in practice is appropriate and meets NICE reference case

requirements. It is therefore unfortunate that the company chose not to use these data at all in the economic model. A similar issue was encountered in NICE TA606 where the ERG commented that some of the limitations with the EQ-5D-5L data collection could have been foreseen and an alternative approach could have been used to capture the impact of HAE attacks on QoL. However, it was agreed that as only 2 out of the 807 attacks recorded in all patients in the trial had an associated EQ-5D score, the data collected were unlikely to capture the QoL impact of HAE attacks and therefore alternative methods had to be considered. To explore this issue further in relation to the APeX-2 trial EQ-5D data, the company was asked to provide further detail on the EQ-5D scores and the number of associated attacks. In their response the company provided EQ-5D scores for the subgroup of patients with ≥2 attacks per month and prior androgen use only, split by whether or not an attack was ongoing at the time of assessment (where ongoing was defined as an attack which began ≤2 days prior to the assessment). See Table 11.

Table 11: Detailed EQ-5D data from APeX-2 (reproduced from Table 16, clarification question B12).

Timepoint	Attack is ongoing at time of assessment				Attack is not ongoing at time of assessment			
	N		Mean EQ-5D score		N		Mean EQ-5D score	
	Berotralstat (n=17)	SoC (n=18)	Berotralstat	SoC	Berotralstat (n=17)	SoC (n=18)	Berotralstat	SoC
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SoC, standard of care

In their response to clarification questions, the company reiterated their view that the EQ-5D data did not capture the QoL impact of either the 'attack' or the 'attack-free' health states in the model due to the small patient numbers in whom an attack was ongoing and the 'unrealistic' results observed. The utility value of [redacted] for SoC patients experiencing an attack at week 12 was highlighted as being clinically implausible. While the ERG agrees the patient numbers are small and there are some counter-intuitive results, this is likely at least in part due to the small sample size and may also reflect the varying severities of attacks as some attacks did not require acute treatment. The ERG does not agree that this justifies discarding the EQ-5D data in its entirety, and believes that it could have been used to inform the average utility loss associated with an attack. Given the concerns about small patient numbers, it is not clear why only data from the subgroup of patients with ≥2 attacks per month and prior androgen use were considered as the QoL of patients experiencing an attack would likely be similar in this particular subgroup compared to the rest of the patient population in the trial. The issues with the APeX-2 QoL data are similar to those identified during TA606;[22] However, even based on the small subgroup data it is clear that more attacks were captured in this study and presumably the number would increase using the full EQ-5D dataset from APeX-2. While there will be limitations with the use of the EQ-5D data, the ERG believes it would be preferable to use these data to inform utility loss associated with attacks, as this would have the important advantage of being measured in patients in the trial which is the main data source for the other inputs in the economic model.

The ERG also does not agree with the company view that the EQ-5D data should not be used to estimate the 'attack free' health state utility value. To address this, the company was asked to provide sensitivity analysis where the QoL of patients in the 'attack free' health state was estimated from the APeX-2 EQ-5D-5L data. In their response to this request, a weighted average of EQ-5D score for patients who were not experiencing an attack at the time of assessment was applied to 'attack-free' patients in the economic model. This resulted in an 'attack-free' utility score of [redacted] and an increase in the ICER to £26,270. It should be noted here that the increase in the ICER compared to the base case is driven by the attack free utility being equalised in both arms (the base case allows the attack rate in the preceding cycle to influence attack free utility).

The ERG concluded a more appropriate approach to deriving utility values for the model would be to use the full ITT EQ-5D-5L dataset to estimate EQ-5D scores for patients in the 'attack-free' and 'attack' health states. This approach should at least have been explored thoroughly. However, an argument could still be made for retaining the small utility benefit for berotralsat in the attack free state based on the attack frequency coefficient from the Nordenfelt study.

Published QoL data used in the economic model

Instead of using EQ-5D data collected in the APeX-2 trial, the company considered two alternative approaches to identify utility values for use in the economic model. A systematic review was conducted which identified 11 studies reporting EQ-5D data. In the base case analysis, utility values from a published study (Nordenfelt et al 2014) were used in the 'attack' and 'attack free' health states.[21] The only justification provided for selecting this study over the others identified in the systematic review is that it was used in TA606. A company-commissioned utility study was used in a scenario analysis.

The Nordenfelt study used data from a retrospective registry of Swedish patients with HAE based on 103 responses from 139 patients who agreed to be contacted (74% response rate). Patients were asked to complete two EQ-5D-5L questionnaires; one to capture QoL 'today' and one based on their last HAE attack. Of the 103 responses included in the analysis, 'today' values were provided by 101 patients and 78 patients reported based on their last HAE attack. Of these, 54 were female (mean age 44 years) and 48 were male (41 years) which shows the patients in the study were comparable with the sub-population of interest within APeX-2 in terms of age (mean age 44 years), but a larger proportion in the trial were female (71.4%).

The mean utility derived from the study for QoL 'today' was 0.825 and during an attack was 0.512. The difference between the two values (0.313) was statistically significant ($p<0.001$) and maintained in mild, moderate and severe attacks. A regression analysis was conducted to estimate the impact of age and frequency of attacks on the utility weights. The study showed that attack frequency and age had a

negative effect on EQ-5D 'today' with patients who had >30 attacks per year (n=11) reporting a significantly lower baseline QoL score equating to a disutility of -0.0043 for each attack in the previous cycle. The impact of age was estimated to be a disutility of -0.02205 per 10 years of age.

The attack free utility value was estimated based on the following formula:

Equation 1: Attack free utility formula used in economic model (reproduced from CS, Document B, page 88)

Attack free utility = 0.825 – 0.02205 x (10 years gained)
– 0.0043 x (number of attacks in previous cycle).

This results in a higher 'attack free' utility value in the berotralstat arm due to the impact of prophylactic treatment in reducing attacks. For the 'attack' health state, an average attack disutility of -0.313 from Nordenfeld (2014) was applied to all attacks for the duration of time patients spend in the 'attack' health state.[21]

The rationale for selecting the Nordenfelt (2014) study for use in the base case analysis was its use in TA606. No comparison was provided of the patient characteristics to demonstrate the study was representative of the relevant patient population. There are some limitations with the study given its retrospective registry design and potential generalisability issues given potential differences in the severity and location distribution of attacks included in the company model. The study also raises questions about the model assumption that location of attack is more relevant than severity in determining patient QoL as the Nordenfelt study suggests increasing severity is associated with a reduction in QoL. While the higher 'attack free' utility value in the berotralstat arm was estimated from the significant negative effect of attack frequency on QoL observed in the study, the ERG notes the small patient numbers this difference in QoL is based on (n=11).

Given these limitations, the ERG does not consider the utility values derived from Nordenfelt to provide more robust estimates of HRQoL for patients with HAE than those derived from the EQ-5D data collected in the APeX-2 trial. Although the

Nordenfelt study was accepted as appropriate in TA606, the justification for excluding the trial-based utility data was stronger given only 2 attacks were captured by the EQ-5D data collection. Sufficient justification has not been provided to exclude the data from APeX-2 in preference for the Nordenfelt study and its associated limitations.

Alternative utility data source

A scenario analysis was conducted using utility values from a time trade-off (TTO) study commissioned by the company. This study recruited [redacted] UK patients with the aim of estimating the QoL impact of HAE on both patients and carers. The study measured attack and attack-free periods, with HAE attacks split into four locations: abdomen, larynx, face, and hand.

A baseline utility value was estimated using the demographics of the TTO population resulting in an age and sex-adjusted utility value of [redacted]. The difference between this value and the TTO ratings are applied as disutilities to the attack-free and attack health states in the model (Table 12).

Table 12: Utility decrements applied in scenario analysis (adapted from table 3 and 4 of Appendix L)

Variable	TTO utility value	Disutility applied in model	Reference
Baseline	[redacted]	[redacted]	
Attack free	[redacted]	[redacted]	TTO study
Abdominal/thoratic attack	[redacted]	[redacted]	TTO study
Limb/other attack	[redacted]	[redacted]	TTO study
Laryngeal attack	[redacted]	[redacted]	TTO study

When the TTO study is used the ICER increases due to the equalising of the attack free utility value in each arm and the smaller attack disutility than that estimated in Nordenfelt.

The TTO study used in the scenario analysis aims to capture location-specific attack disutilities, which may closer reflect the variation in the HRQoL impact of HAE attacks than applying a single attack disutility. It can also be considered a more conservative analysis due to removing the QoL benefit for berotralstat in the 'attack free' health state and a smaller utility decrement for attacks. However, there are some important limitations with this study. It is an unpublished, company-sponsored study and full methods and results have not been provided. The study relied on health state vignettes, whereas the NICE reference case favours the measurement of health related quality of life being reported directly by patients and carers. Despite these limitations, it is helpful to see the impact of location-specific disutilities as a sensitivity analysis.

Caregiver disutility

The company made the case that the carers of patients with HAE are impacted during an attack and included a caregiver disutility to account for this in the model. As the Nordenfelt study used to estimate patient utility values did not capture

caregiver disutilities, the caregiver disutility estimate from the TTO study was used ([redacted]). This was said to reflect the impact on caregivers' QoL due to anxiety and need to provide physical assistance during attacks. This disutility was applied in the model for all time spent experiencing an attack in the alive health state for all patients in each cycle.

In relation to the inclusion of the QoL impact on carers, the NICE Reference Case states that "all direct health effects, whether for patients, or when relevant, carers" should be considered. However, the NICE Decision Support Unit (DSU) conducted a review of carer utilities which found that <3% of published NICE TAs quantitatively estimated carer disutilities and those that did were often limited by poor quality data. The majority of TAs where carer utilities were included were for MS, Alzheimers and paediatric treatments, but the review noted that it was unclear whether carer burden is significantly greater in these disease areas relative to other conditions. However, when carer utility was quantitatively estimated, most appraisals included it in decision-making either in the base case or sensitivity analysis.

The ERG agrees it is reasonable to consider the QoL impact of HAE attacks on carers, but does not consider a strong case has been made to include these data in the base case analysis. It is also noted that no carer disutilities were included in TA606. In addition to the limitations with the TTO study used to estimate carer disutility noted above, the application of a single value for every attack, for every patient, may be too simplistic. The company stated that attack severity will vary and data from APeX-2 shows that some attacks did not even require acute treatment. As such, it seems unlikely that all attacks will impact on carers QoL, at least not to the same extent. The magnitude of carer disutility ([redacted] per attack) seems large when compared to the range identified in the DSU review of NICE TAs (0.01 to 0.173 per year). Given these uncertainties, the ERG believes the inclusion of carer disutility in the base case would benefit from further justification in terms of rationale and approach. When carer disutility is excluded the company's ICER increases to £27,461 (see 5.3 below).

<u>Mode of administration utility benefit</u>

In the base case analysis no additional utility benefit was included to capture patient preferences for different modes of administration, but this was explored in a scenario analysis using data from a published study (Holko 2018) that examined the QoL impact of oral, SC and IV administration of treatment for inflammatory bowel disease. In the scenario analysis, utility decrements are applied for all attacks to capture the additional QoL impact of receiving SC treatments (-0.147). As berotralstat is estimated to reduce the number of attacks, applying this additional attack disutility results in a significant reduction in the ICER.

The company argues that excluding the mode of administration disutilities for SC and IV treatments may underestimate the benefit of berotralstat as it is an oral treatment. However, what the scenario analysis does is explore the impact of increasing the attack disutility due to the use of treatments that require SC or IV administration. This appears to assume that the Nordenfelt study does not capture the QoL impact of requiring SC or IV treatments for acute attacks. While this may be the case, no specific data are provided to show how often HAE patients have problems with SC or IV administration and therefore to assume this occurs with every acute treatment is likely to be an overestimate. The ERG noted that the utility impact of administration route and frequency were explored in TA606 but the values used are difficult to compare as it was specifically related to the different administration routes for prophylactic treatment. For information, a utility increment of 0.024 was applied to patients in the lanadelumab arm due to SC administration compared with IV administration in the comparator arm.

The ERG agrees with the company that the impact of mode of administration on utility should not be included in the base case analysis.

4.2.8 Resources and costs

The costs and resource use included in the model can be split into three main categories: prophylactic treatment and administration costs, acute treatment and administration costs, and resource use associated with acute attacks.

Prophylactic treatment costs: berotralstat

The recommended dose of berotralstat for adults and adolescents aged 12 years and older is 150mg capsule taken once daily. As berotralstat is an oral treatment no administration costs are included. The cost of a 28 capsule pack is given in table 13 along with the cost per cycle, day and year. A patient access scheme (PAS) has been agreed in the form of a [redacted].

Table 13: Acquisition costs of berotralstat with PAS discount (reproduced from Table 30, Document B, pg 92)

Variable	Cost	
Price per pack with PAS discount	[redacted]	
Cost per day	[redacted]	
Cost per 28-day cycle	[redacted]	
Annual cost	[redacted]	

The cost per cycle is applied to patients in the berotralstat arm in the model. Note that a continuation rule is applied where non-responders discontinue treatment at 3 months and only responding patients with a 50% reduction in attack frequency from baseline continue on berotralstat for the remainder of the model. No prophylactic treatments are included in the SoC arm as this was assumed to include only acute treatment for HAE attacks. Note, an adjustment for compliance ([redacted]) is applied to the cost of berotralstat in the company model based on the APeX-2 trial. This wasn't discussed in the company submission.

Acute treatment

The cost of treating acute attacks is included in both the berotralstat and SoC arms of the model. Four treatments are licensed to treat acute HAE attacks in the UK: C1-INHs (Berinert and Cinryze), icatibant (Firazyr) and conestat alfa (Ruconest). Drug acquisition costs are taken from the BNF.

Berinert uses weight-based dosing at a rate of 20IU/kg and is available in 500 or 1500 unit vials. The mean dose of Berinert is estimated using the mean weight of patients in the APeX-2 trial subgroup (86.41kg) resulting in a mean dosage of

1728.21 units. This was used to estimate a cost per administration of £1,901 excluding wastage. The costs of Berinert and the other acute treatments are summarised in Table 14 below. No administration costs are included for acute treatments as all are assumed to be self-administered at home.

Table 14: Summary of acute treatment costs (adapted from Table 32 of Document B)

Acute treatment	Dose/ administration	Vials/ POMs available	Number of vials/ POMs	Cost per vial/POM	Cost/ administration	Notes
C1-INH (Berinert)	1728.21 units (based on weight of 86.41kg)	500 or 1500 unit vials	2	£550 (500 units) £1,650 (1,500 units)	£1,901	Wastage not included
C1-INH (Cinryze)	1000 IU	500 unit vials	2	£1,336 for 2 vials	£1,336	Wastage N/A
Icatibant (Firazyr)	30mg	30mg/3ml POM	1	£1,395	£1,395	Wastage N/A
Conestat alfa (Ruconest)	4200 units for patients ≥84kg	2100 unit vials	2	£750	£1,500	Wastage N/A

N/A = no applicable, POM = pre-filled disposable injection, C1-INH = C1-esterase inhibitor

In order to estimate the cost of acute treatment, the observed rates of acute treatment use from the APeX-2 trial were applied. The company argued there is variation in attacks such that some require treatment and others do not. The proportion of attacks treated in the model is based on the rates observed in the APeX-2 trial (see Table 6). The resource use collected in the trial show some attacks required multiple administrations of acute treatment, which the company says reflects how patients are treated in practice. The company noted that previous HAE

appraisals did not account for multiple administrations and therefore underestimated the costs of acute attacks. An alternative scenario was conducted in the sensitivity analysis using UK clinical opinion to estimate usage of acute treatments. The base case (APeX-2) and scenario analysis (UK clinical opinion) rates are summarised in Table 15.

Table 15: Acute therapy usage from APeX-2 and clinical expert opinion (adapted from table 31, document B and table 6, Appendix L)

Treatment	APEX-2		UK Clinical opinion (number of doses not specified)
	Berotralstat	SoC	
Total treated for acute attack	[redacted]	[redacted]	[redacted]
Total treated with 1 dose	[redacted]	[redacted]	[redacted]
• Berinert (C1-esterase inhibitor) 1 dose	[redacted]	[redacted]	[redacted]
• Cinryse (C1-esterase inhibitor) 1 dose	[redacted]	[redacted]	[redacted]
• Firazye (icatibant) 1 dose	[redacted]	[redacted]	[redacted]
• Ruconest (Recombinant C1-esterase inhibitor) 1 dose	[redacted]	[redacted]	[redacted]
Total treated with multiple doses	[redacted]	[redacted]	[redacted]

Using the treatment usage rates from APeX-2, the cost per acute attack was calculated by treatment arm as summarised in Table 16.

Table 16: Average acute treatment cost per attack

Treatment arm	Average acute treatment cost per attack	Reference
Berotralstat	[redacted]	APeX-2 and BNF
SoC	[redacted]	APeX-2 and BNF

The estimated cost per attack is higher in the SoC arm, which the company said was due to the reduced need for multiple administrations of acute treatments in the berotralstat arm compared with SoC. The different acute treatment costs per arm are applied to the proportions requiring acute treatment in the trial.

The concern with the application of acute attack costs in the model is the different attack cost applied in each arm. Clinical advice to the ERG did not support the company's explanation that the lower cost in the berotralstat arm was due to the 'reduced need for multiple administrations' for patients treated with prophylactic berotralstat. The ERGs clinical advisor did not identify a plausible clinical reason for prophylactic treatment to consistently or predictably impact on the cost of treating acute attacks. It is possible that the different costs in each arm arising from the use of the APeX-2 acute treatment distribution is due to random variation because of the small patient numbers in the subgroup used to inform the model (n=35 patients: 17 berotralstat, 18 SoC; [redacted]). Whilst a difference was maintained in the larger subgroup that experience ≥ 2 attacks per month at baseline, it might have been helpful to calculate and formally compare the cost per attack using the ITT population to provide further justification for applying a difference between arms and to better inform the absolute magnitude of the costs (assuming attack treatment costs are generalisable across subgroups). Taking an average of the two attack costs applied in the company base case, and applying it in both arms results in a cost of [redacted] per attack which increases the ICER to £99,828 *(includes correction of minor bugs in company base case – see section 6.3).*

An additional issue was identified with the face validity of acute treatment estimates from the trial. As summarised in Table 6 above, a proportion of patients in both arms required multiple administrations of acute treatments to resolve symptoms. However,

the ERG clinical expert view was that a high-frequency, basal requirement for multiple administrations to treat individual acute attacks would not be the recognised norm in UK clinical practice. The company did explore a scenario analysis using the estimates of acute treatment usage from UK clinical experts (see Table 6 above). The company noted that the responses from UK experts indicate a higher use of treatments commonly associated with multiple administrations (e.g. icatibant) and therefore concluded the application of the APeX-2 trial rates in the base case is conservative. However, the usage rates informed by clinical experts were derived through discussion at an advisory board meeting and are difficult to compare with the usage rates in APeX-2 as information on the proportion of attacks requiring treatment or the proportion requiring multiple doses is not provided. It is also not clear how this alternative approach was applied in the model sensitivity analysis. Appendix L states the rates of administration from APeX-2 were used but the costs adjusted to account for the difference in usage patterns estimated by UK clinical experts. Further detail on this scenario analysis would be helpful.

An issue was identified in the estimate of the cost of Berinert. In the base case, the mean weight of patients in the trial was used. For accuracy, it may be preferable to calculate the acute treatment dose required for each patient in the trial, then calculate individual acute treatment costs based on the number of vials required for each patient, and then take the average cost. Following clarification, the company provided this in a scenario analysis which resulted in an average cost per administration of £1,843.89. This higher cost increased the ICER to £24,278.

Health state unit costs and resource use

Resource use associated with HAE attacks is included in the model based on input from 8 UK clinical experts identified by the company. A systematic literature review was conducted to identify published studies reporting cost and resource use associated with HAE but none of the identified studies are used in the model. Resource use included A&E visits, hospitalisation, intubation, radiography, ambulance transport and blood tests. As resource use is likely to vary by attack, the company used attack location to identify different costs as a proxy for attack severity. This was due to attack location being considered more objective than severity of

attack, which was patient-defined in APeX-2. The resource use estimates used in the model are summarised in Table 17.

Table 17: Acute attack resource use requirements (reproduced from Table 34, Document B)

Health care resource use	Abdominal/thoratic attack	Limb/other attack	Laryngeal attack
• Proportion of patients requiring a visit to A&E	[redacted]	[redacted]	[redacted]
• Proportion of patients requiring hospitalisation	[redacted]	[redacted]	[redacted]
• Number of days for inpatient stays	[redacted]	[redacted]	[redacted]
• Proportion requiring intubation	[redacted]	[redacted]	[redacted]
• Proportion who receive radiography	[redacted]	[redacted]	[redacted]
• Proportion requiring ambulance transport	[redacted]	[redacted]	[redacted]
• Proportion requiring blood test	[redacted]	[redacted]	[redacted]
• Number of blood tests	[redacted]	[redacted]	[redacted]

Resources were valued using unit costs from PSSRU or NHS reference costs (see CS, Document B, Table 35).[28, 29] Of note, the selected inpatient cost per day of £454 (NHS reference cost, WJ11Z non-elective short stay) is consistent with the preferred cost per day selected by the ERG in TA606. The acute attack resource use costs were estimated by treatment arm, weighted by the proportions of attacks in

each location (see CS, table 27). The majority of attacks were limb/other ([redacted] in the berotralstat and SoC arms respectively). The average resource use cost per acute attack was estimated at [redacted] respectively.

As noted previously, adverse events were not included in the model as it is assumed, given the safety profile of berotralstat, the impact of adverse events on the model is negligible. The ERG notes that the exclusion of adverse event treatment costs may introduce a small bias in the model in favour of berotralstat, but as all TEAEs were mild or moderate any impact is likely to be small.

The attack resource use estimates are lower than those estimated in TA606 where a cost per attack of £95 was estimated. Length of stay and proportion of patients requiring A&E and hospital admission are broadly comparable. The key issue is that the different resource use costs estimated by treatment arm may be a result of random variation due to small patient numbers in the subgroup and might not be realised in clinical practice. Similar to the issue in the estimation of acute treatment costs, the ERGs clinical advisor did not identify a plausible clinical reason for the cost of an attack to be consistently influenced by the prophylactic treatment patients are receiving. The ERG considers applying the same average resource use cost per treatment arm as an appropriate scenario, as the company has not provided strong evidence or clinical arguments to support a difference. The use of the ITT population again could provide more robust data for this model parameter. Sensitivity analysis was conducted using an average cost per attack pooled across the two treatment arms of [redacted]. This increased the ICER to £24,759 (includes correction of minor bugs in company base case – see section 6.3).

Finally, there is some uncertainty regarding the number of attacks observed in the subgroup used to estimate costs and utility values in the model due to inconsistency in reporting of these figures in the company's response to the clarification questions. In table 13 of their response the total number of attacks is [redacted] and [redacted] *in the berotralstat and SoC arms respectively. This is inconsistent with table 19 of the response document where the number of attacks requiring treatment are* [redacted] *and* [redacted] *respectively. The reason for the discrepancy is not clear to the ERG.*

5 COST EFFECTIVENESS RESULTS

5.2 Company's cost effectiveness results

The company's base case ICER is provided in Table 39 of the company submission (document B, section B.3.7). Applying the discounted price for berotralstat, and undiscounted prices for drugs used to treat acute attacks, the company base case ICER comes to £20,707 per QALY gained versus SoC. This is based on an incremental cost of [redacted] for an incremental QALY gain of [redacted]. The incremental cost is driven by the prophylactic berotralstat treatment costs of [redacted] per patient minus attack treatment cost savings of £[redacted] per patient over the lifetime horizon. The incremental QALY gain, driven by the reduction in attack rate with berotralstat, is made up of increased patient QALYs of [redacted] ([redacted]) and increased carer QALYs of [redacted] ([redacted]) versus SoC.

5.3 Company's sensitivity analyses

The company undertook deterministic one-way sensitivity analysis (see Figure 14 and Table 41 of the CS, document B), which showed the model results to be most sensitive to (top 6): 1) baseline attack rate for SoC, 2) the proportion of attacks treated in the SoC arm, 3) the berotralstat price per cycle, 4) berotralstat compliance (used to adjust treatment cost), 5) the percentage reduction in attack rate applied in the berotralstat arm from month 12, and 6) the Firazyr (icatibant) cost per attack.

Whilst useful in showing what the model is sensitive to, some of the one-way variation tested lacks clinical plausibility. For example, the ERG believes that it is inappropriate to vary the baseline attack rate in one arm and not the other.

The company also undertook several scenario analyses, presented in Table 42 of the CS. The ERG was of the opinion that these did not address all the of the uncertainties inherent in the company's model structure and choice of data to inform inputs. Therefore, the ERG requested some further scenario analyses in the

clarification letter which the company subsequently provided. The additional scenarios were as follows:

1. (Question B4) For extrapolation beyond the observed follow-up period of APeX-2, application of the average monthly attack rate observed across months 0-6 for the relevant subgroup of patients in the placebo arm of APeX-2 (for SoC), and the average monthly attack rate observed across months 4-12 for responders in the relevant subgroup of patients in the berotralstat 150mg arm.
2. (Question B5) Application of the pooled baseline attack rate from the relevant subgroup of APeX-2 in both arms of the model, rather than baseline attack rates specific to each treatment arm.
3. (Question B8d) A scenario whereby the percentage reductions from baseline for berotralstat responders are calculated using the baseline attack rate for this restricted group, rather than the average baseline attack rate for the subgroup as a whole (which includes non-responders).
4. (Question B11) Removal of carer disutility
5. (Question B13) Application of the EQ-5D data from the APeX-2 trial for the 'attack free' health state
6. (Question B15) Application of berinert attack treatment costs using the number of vials required to treat each patient with the recommended weight-based dosing (assuming no vial sharing).
7. (Question B16) A probabilistic sensitivity analysis that uses actual standard errors for attack rate percentage reductions based on the trial data, rather than assuming 10% of the mean to represent standard errors.
8. (Question B17) Scenario analyses varying the acute attack treatment costs, eluded to in Section B.2.8.3 of the CS (document B), but not reported in Table 42 of the CS.
9. (Question B18) The treatment waning scenario analyses in which the effect of treatment waning for berotralstat occurs at 5, 10 and 20 years. These were mentioned in Appendix L of the CS, but the results were not provided in the original submission.
10. (Question B22) Scenario analyses whereby all model inputs are informed by the overall trial population - under the assumption that the percentage

reduction in attack rates from baseline, the distribution of attack location and duration, and distribution of attack treatments are generalisable to the company's positioning (≥2 attacks per month and previous experience of androgens). A further scenario that combined these changes with those requested in clarification question B4 (see 1 above) and clarification question B8 (see 3 above) was also requested.

The company provided the results for these scenarios as summarised in Table 18 below. As well as providing the scenario requested in clarification question B4 (Table 18, 1b below), the company provided an alternative scenario whereby the baseline attack rate in the SoC arm was applied throughout the model, and the average attack rate over months 4-12 was applied for berotralstat responders (Table 18, 1a). Both scenarios substantially increased the ICER.

Regarding the equalisation of baseline attack rates to the pooled value (Table 18, 2), this change favoured berotralstat since the baseline attack rate was highest in the berotralstat arm in the company base case.

For the response to clarification question B8d (scenario 3 in Table 18 below), this was not implemented as the ERG had intended. The company applied the baseline attack rate for berotralstat responders to the berotralstat arm of the model, and then applied the percentage reductions for responders from month 1 onwards. The ERG had indented for the percentage reductions for responders to be recalculated relative to the baseline attack rate of responders, and then applied to the overall baseline attack rate from month 4 in the model, the timepoint from which only responders continue treatment. This was to factor out random variation in the baseline attack rate between responders and non-responders.

For the response to clarification question B22, the company provided scenarios demonstrating the cumulative impact of several stepped changes (Scenarios 10a – 10e in Table 18 below). As discussed above, the company provided these scenarios with inputs based on the larger subgroup of those experiencing ≥2 attacks per month at baseline, rather than the ITT population (with percentage reductions applied to the

mean baseline attack rate of the proposed positioning) as the ERG had originally intended.

Using the data from the larger subgroup experiencing ≥2 attacks per month at baseline, but otherwise applying the same structural assumptions as per the company's base case, the ICER for berotralstat increased substantially (Table 18, 10a). When holding the SoC attack rate constant at the baseline value (Table 18, 10b), the ICER improved relative to 10a, indicating that the attack rate observed at six months for the larger subgroup in the placebo arm of APeX-2, was lower than the baseline value. When then applying the average percentage reduction in the monthly attack rate for berotralstat responders beyond month 12, the ICER improved slightly (Table 18, 10c). However, when applying the average percentage reduction in the monthly attack rate observed over months 0-6 for the larger subgroup in the placebo arm of APeX-2, to the SoC arm of the model, the ICER increased again substantially (Table 18, scenario 10d). Finally, the company provided a scenario with model inputs based on the subgroup of APeX-2 experiencing 2 attacks or more per month at baseline (as per 10a), but with the baseline attack rate for responders applied to the berotralstat arm of the model, and the percentage reductions for responders applied from month 1 onwards (Table 18, 10e). However, as outlined above for the company response to clarification 8d, this was not what the ERG had intended.

The ERG believes that these further requested scenarios highlight the substantial uncertainty in the company's cost-effectiveness case, driven by uncertainty around the most appropriate extrapolation assumptions to apply and the choice of data to inform the model inputs. The substantial increases in the ICER observed when informing inputs using data from the larger subgroup of patients in APeX-2 with ≥ 2 attacks per month at baseline, without clear clinical rationale for why these inputs should differ according to prior androgen use, raises concerns that the company's lower base case ICER is a chance finding resulting from model inputs being informed by a small post-hoc subgroup of APeX-2.

Table 18: Summary of ERG requested scenarios conducted by the company (reproduced from Table 26 of the company's response to the clarification letter)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
1. a) B4 (SoC baseline attack rate applied throughout)								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	127,503	127,503
1. b) B4 (average attack rates applied)								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	230,289	230,289
2. B5 (pooled attack rate)								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant
3. B8d (responder baseline attack rate and reductions applied)								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,616	14,616
4. B11 (caregiver disutility excluded)								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,461	27,461
5. B13 (attack-free EQ-5D)								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	26,270	26,270
6. B15 (individual berinert administration applied)								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-

Berotralstat	[redacted]						24,278	24,278
7. B16 (actual standard errors) – Probabilistic results								
SoC	[redacted]						-	-
Berotralstat	[redacted]						60,039	60,039
8. B17 (Acute costs +10%)								
SoC	[redacted]						-	-
Berotralstat	[redacted]						Dominant	Dominant
8. B17 (Acute costs -10%)								
SoC	[redacted]						-	-
Berotralstat	[redacted]						114,411	114,411
9. B18 (Treatment waning: 5 years)								
SoC	[redacted]						-	-
Berotralstat	[redacted]						55,400	55,400
9. B18 (Treatment waning: 10 years)								
SoC	[redacted]						-	-
Berotralstat	[redacted]						37,182	37,182
9. B18 (Treatment waning: 20 years)								
SoC	[redacted]						-	-
Berotralstat	[redacted]						26,243	26,243
10. a) B22 (≥2 attacks per month)								
SoC	[redacted]						-	-
Berotralstat	[redacted]						261,714	261,714
10. b) Alternative B22 (≥2 attacks per month, SoC baseline attack rate applied thoughout)								
SoC	[redacted]						-	-
Berotralstat	[redacted]						148,299	148,299
10. c) B22 & B4 (≥2 attacks per month; berotralstat mean attack rate, SoC baseline attack rate applied thoughout)								
SoC	[redacted]			-	-	-	-	-

Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	143,566	143,566
10. d) B22 & B4 (≥2 attacks per month; berotralstat mean attack rate, SoC mean attack rate)								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	391,357	391,357
10. e) B22 & B8d (≥2 attacks per month; responder baseline attack rate applied)								
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	254,743	254,743

5.4 Model validation and face validity check

The CS states that an advisory board comprised of eight UK consultant immunologists was used to validate modelling assumptions, provide estimates for the resource use associated with attacks, and to inform the positioning of berotralstat within the treatment pathway. In addition, the CS states that all key modelling assumptions were validated by independent UK health economics experts. A Delphi panel process was used to generate consensus from the advisory board for the parameters used to inform the continuation rule.

The ERG has undertaken a range of further verification tests, based on an adaption of those proposed by Tappenden et al. Examples of the black-box checks are reported in Appendix 1, applied to the company preferred base case analysis. The ERG identified an inconsistency in the formulae used to calculate caregivers' QALYs within the berotralstat Markov trace sheet between columns *BI* and *BP* (also used in the placebo Markov trace sheet). The ERG understood this as to be an error in the formula applied to those on berotralsat (Worksheet "Trace Berotralstat", cells BI14 to BI772), and correct this to align with the one used for those on standard care. The original formula underestimated the caregiver utility loss for those on berotralstat, and therefore the ERG correction resulted in a modest increase in the ICER. The company also corrected two percentage reductions from the baseline attack rate experienced in months 4 and 5 for berotralstat responders. All the ERG further analysis used the fully corrected version of the model.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Based on the issues identified in the preceding sections, the ERG undertook some further scenarios analysis using the company's model as follows, with the results provided in Table 19 below:

0. Company base case (note, includes a correction to the percentage reduction from baseline attack rate experienced in months 4 and 5 for responders, which the company made when they responded to the clarification letter).
1. Correction of the carer QALY formula identified by the ERG in the economic model for those on belotrastat ('Trace Berotralstat'!BI14:BI772). This provides the reference base for all other scenarios in Table 19.
2. Equalised baseline attack rates ([redacted] per month for berotralstat and placebo arm)
3. Calculation of percentage reductions for responders relative to the baseline attack rate for responders, but applied to the fixed baseline attack rate for the subgroup as a whole (from month 4)
4. Average percentage reduction in attack rate between months 4 and 12 for berotralstat responders carried forward beyond month 12 ([redacted]
5. Baseline attack rate carried forward for SoC throughout the model time horizon (0% reduction from baseline attack rate applied throughout)
6. Average attack rate over months 0-6 carried forward for SoC beyond month 6 ([redacted]
7. Equalisation of attack treatment costs between the treatment arms (applied as a flat average of the total cost per attack in each arm ([redacted])
8. Equalisation of health care resource use costs between treatment arms ([redacted]).
9. Assess the impact of setting compliance parameter to 100%
10. Combination of scenarios 1, 2, 3, 4 and 6
11. Combination of scenarios 1, 2, 3, 4, 6 and 7
12. Combination of scenarios 1, 2, 3, 4 and 5
13. Combination of scenarios 1, 2, 3, 4 and 6 but with all inputs informed by the larger subgroup of those experiencing ≥ 2 attacks per month at baseline (inclusive of those without experience of androgens)

14. Combination of scenarios 1, 2, 3, 4 and 5 but with all inputs informed by the larger subgroup of those experiencing ≥ 2 attacks per month at baseline (inclusive of those without experience of androgens)
15. Carer disutility of attacks reduced by half (from [redacted])
16. Carer disutility removed.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The impact of each individual change assessed by the ERG can be seen in Table 19. Correcting the inconsistency in the formula used to apply carer QALY losses, resulted in small reduction in incremental QALY gain for berotralstate (from [redacted]). The ICER correspondingly increased from £20,721 to £21,129. The equalisation of baseline attack rates between arms notably improves the ICER for berotralstat, as this parameter disadvantages it in the company base case. However, the other changes work in the opposite direction. The greatest impacts on the ICER can be seen with the equalisation of baseline attack rates (scenario 2), changes to the extrapolation assumptions (scenarios 4, 5 and 6), equalisation of acute treatment costs (scenario 7), and the use of data from the larger subgroup to inform the model inputs (scenario 13 versus scenario 10).

6.3 ERG's preferred assumptions

Given the small numbers and variability in monthly attack rates observed over follow-up in both the placebo arm subgroup and the berotralstat responder subgroup used to inform long-term attack rates in the model, the ERG has a preference towards carrying forward the relevant average monthly attack rates (scenarios 4 and 6) over the last observation carried forward or the baseline attack rate for the placebo arm carried forward. This guards against random variation leading to exaggeration of the relative reduction in attack rate for berotralstat responders versus SoC. However, the ERG acknowledges the uncertainty inherent in any extrapolation approach, and would welcome further consultation on the most appropriate assumptions for the model.

Regarding other changes, the ERG has a clear preference for equalising baseline attack rates between treatment arms to factor out the influence of random between

arm variation in this parameter (scenario 2). Similarly, the ERG prefers to use percentage reductions for responders that are calculated relative to the baseline rate for this restricted subgroup, but then applied to a fixed baseline rate that is equalized between arms. This leads to scenario 10 in Table 19 offering the preferred ERG base case when using data from the subgroup of APeX-2 with ≥ 2 attacks per month at baseline and prior experience of androgens. It can be noted that equalising acute treatment costs per attack on top the ERG preferred assumptions (scenario 11) also results increases in the ICER further, as would reducing or removing the carer disutility for attacks. The ERG believes that both of these issues would benefit from further justification and consultation, but retains the company approach its base case for now.

To assess uncertainty regarding the data used to inform the model inputs, scenario 13 shows the impact of changing inputs to those based on data from the larger subgroup of APeX-2 with ≥ 2 attacks per month at baseline. It should be noted that as well as percentage reductions from baseline changing with this scenario, parameters including the baseline attack rate, duration of attacks, location of attacks, and acute treatment distributions are also updated based on the data for the larger subgroup in this analysis. The Table of revised inputs provided by the company for analyses based on the ≥2 attack per month subgroup is provided Appendix 1.

Finally, to assess the uncertainty related to the extrapolation assumptions in the ERG base case, alternative combined scenarios are provided whereby the baseline attack rate is carried forward for SoC in combination with the ERGs other preferred assumptions. These scenarios are applied for inputs based on both the smaller subgroup (≥ 2 attacks per month at baseline and prior androgen use) (scenario 12) and the larger subgroup (≥ 2 attacks per month at baseline) (scenario 14).

Table 19 Results of exploratory analysis undertaken by the ERG

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
0	Company Base Case							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,721
1	Company Base Case (corrected)							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,129
	ERG Further analyses							
2	Equalised baseline attack rate for berotralstat & placebo							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
3	Berotralstat: application of percentage reductions for responders relative to the baseline attack rate for responders (from month 4)							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,786
	Extrapolations							
4	Berotralstat: average attack rate between months 4 and 12 for responders to be carried forward							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	61,743
5	SoC: baseline attack rate to be carried forward							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	85,063

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
6	SoC: average attack rate over months 0-6 to be carried forward							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	182,524
7	Equalisation of attack treatment costs between the arms							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	99,828
8	Equalisation of health care resource use costs between treatment arms							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,837
9	Assess impact of setting compliance parameter to 100%							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,226
10	Combined scenarios: 1, 2,3, 4, & 6 (ERG preferred base case							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	160,308
11	Combined scenarios: 1, 2,3, 4, 6 and 7 (ERG preferred base case) + equalised treatment costs							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	246,624
12	Combined scenarios: 1, 2,3, 4, and 5							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	62,285
13	≥ 2 attacks subgroup & preferred ERG assumptions (combined scenarios: 1, 2,3, 4, & 6)							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	352,311
14	≥ 2 attacks subgroup & combined scenarios: 1, 2,3, 4, & 5							

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	108,446
15	Carer disutility due to attack reduced by half (from [redacted])							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,883
16	No carer disutility							
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
	Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,461

6.4 Conclusions of the cost effectiveness section

Overall, the ERG believes there is substantial uncertainty surrounding the cost-effectiveness case. Plausible changes to several key parameters result in substantial increases from company's base case ICER. Whilst acknowledging the company's reasoning for basing the model parameters on the subgroup of APeX-2 that most closely matches the proposed positioning, this has led to the model inputs being based on small numbers of patients and events. In the ERGs opinion, it may be possible to make better use of the available data from APeX-2 by carefully considering which model parameters are generalisable from the ITT population, or the larger subgroup of those experiencing ≥ attacks per month at baseline, to the subpopulation of the proposed positioning.

Key issues in the cost-effectiveness case that the ERG believe would benefit from further consultation and evidence, as detailed in the Executive summary, include:

- The selection of data from APeX-2 used to inform key model inputs
- The method used for the extrapolation of attack rates beyond the follow-up period of the trial
- The characterization of uncertainty around the ICER (PSA) given the small numbers and the model structure
- Further consideration of the potential for the "attack" and "attack free" utilities to be informed by analysis of APeX-2 EQ-5D data
- The inclusion of and assumptions around the incorporation of carer disutility in the model
- The attack costs applied in each arm of the model.

7 END OF LIFE

The company indicate that berotralstat does not meet the criteria for life-extending treatment at the end of the life. The ERG concurs with the company’s view.

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Appendix 1 Verification checks on the company's model

Table A1 'Black box' verification checks conducted on the company submitted model

Model component	Model test	Unequivocal criterion for verification	Issues identified
Clinical trajectory	high and low attack reduction values for berotralstat and placebo groups	ICER moving in the expected direction (e.g. higher reductions for berotralstat favor berotralstat; lower favor placebo)	None
	Sum health state occupancy at any model timepoint	Total probability equals 1.0	None
QALY estimation	Set all health utility for living states parameters to 1.0, set all adverse event disutilities to 0, set discount rate QALY = 0	QALY gains equal LYGs	None
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments & no impact on costs	None
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero for all treatments	None
Cost estimation	Set berotralstat costs to 0	ICER is reduced (berotralstat dominant)	None
	Increase intervention cost	ICER is increased	None
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	None
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	None
General	Check Markov traces and equations	Consistent formulas between berotralstat and placebo and/or between similar	Inconsistent formula for the calculation of QALYs for career within the baerotralstat Markov

		columns within each Markov trace	trace (columns BI and BP). Corrected. ICER for CS base case increased.
	Amend value of each individual model parameter*	ICER is changed	None
ICER incremental cost-effectiveness ratio, LYG life-years gained, QALY quality-adjusted life-year			

Appendix 2: model parameters for patients with ≥2 attacks at baseline

The clinical parameters informed by the population of patients with ≥2 attacks at baseline are presented in Table A2.

Table A2: Clinical parameters used to inform the ≥2 attacks at baseline population (Source: Company's second response to the ERG clarification letter to the company)

Clinical parameter	Berotralstat	SoC
Weight (kg)	[redacted]	
Proportion of female	[redacted]	
Baseline age	[redacted]	
Mean duration of all attacks (hours)	[redacted]	[redacted]
Proportion of laryngeal attacks	[redacted]	[redacted]
Proportion of Abdominal/thoratic attacks	[redacted]	[redacted]
Proportion of Limb/other attacks	[redacted]	[redacted]
Any single use of Berinert	[redacted]	[redacted]
Any single use of Cinryze	[redacted]	[redacted]
Any single use of Firazyr	[redacted]	[redacted]
Any single use of Ruconest	[redacted]	[redacted]
Any double use of Berinert	[redacted]	[redacted]
Any double use of Cinryze	[redacted]	[redacted]
Any double use of Firazyr	[redacted]	[redacted]
Any double use of Ruconest	[redacted]	[redacted]
Any third use of Berinert	[redacted]	[redacted]
Any third use of Cinryze	[redacted]	[redacted]
Any third use of Firazyr	[redacted]	[redacted]
Any third use of Ruconest	[redacted]	[redacted]
Any fourth use of Cinryze	[redacted]	[redacted]
Any fourth use of Firazyr	[redacted]	[redacted]
Any fifth use of Firazyr	[redacted]	[redacted]
Any sixth use of Firazyr	[redacted]	[redacted]
Any seventh use of Firazyr	[redacted]	[redacted]
Any tenth use of Firazyr	[redacted]	[redacted]

Any use of Berinert	[redacted]	[redacted]
Any use of Cinryze	[redacted]	[redacted]
Any use of Firazyr	[redacted]	[redacted]
Any use of Ruconest	[redacted]	[redacted]
Berotralstat compliance	[redacted]	[redacted]
Baseline attack rate	[redacted]	[redacted]
Attack rate percentage change from baseline: Month 1	[redacted]	[redacted]
Attack rate percentage change from baseline: Month 2	[redacted]	[redacted]
Attack rate percentage change from baseline: Month 3	[redacted]	[redacted]
Attack rate percentage change from baseline: Month 4	[redacted]	[redacted]
Attack rate percentage change from baseline: Month 5	[redacted]	[redacted]
Attack rate percentage change from baseline: Month 6	[redacted]	[redacted]
Attack rate percentage change from baseline: Month 7	[redacted]	[redacted]
Attack rate percentage change from baseline: Month 8	[redacted]	[redacted]
Attack rate percentage change from baseline: Month 9	[redacted]	[redacted]
Attack rate percentage change from baseline: Month 10	[redacted]	[redacted]
Attack rate percentage change from baseline: Month 11	[redacted]	[redacted]
Attack rate percentage change from baseline: Month 12	[redacted]	[redacted]
Baseline attack rate (responders)	[redacted]	[redacted]
Attack rate percentage change from baseline (responders): Month 1	[redacted]	[redacted]
Attack rate percentage change from baseline (responders): Month 2	[redacted]	[redacted]

Attack rate percentage change from baseline (responders): Month 3	[redacted]	[redacted]
Attack rate percentage change from baseline (responders): Month 4	[redacted]	[redacted]
Attack rate percentage change from baseline (responders): Month 5	[redacted]	[redacted]
Attack rate percentage change from baseline (responders): Month 6	[redacted]	[redacted]
Attack rate percentage change from baseline (responders): Month 7	[redacted]	[redacted]
Attack rate percentage change from baseline (responders): Month 8	[redacted]	[redacted]
Attack rate percentage change from baseline (responders): Month 9	[redacted]	[redacted]
Attack rate percentage change from baseline (responders): Month 10	[redacted]	[redacted]
Attack rate percentage change from baseline (responders): Month 11	[redacted]	[redacted]
Attack rate percentage change from baseline (responders): Month 12	[redacted]	[redacted]
Weighted average	[redacted]	[redacted]