NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

# Committee Papers

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

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The **final scope** and **final stakeholder list** are available on the NICE website.

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NICE National Institute for Health and Care Excellence

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

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

# Berotralstat for the prevention of recurrent attacks of hereditary angioedema [ID1624]

## Document B

## Company evidence submission

**December 2020**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| **Berotralstat in HAE - NICE Submission - Document B FINAL.docx** | **FINAL** | **Yes** | **8th Dec, 2020** |

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Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

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# B.1. Decision problem, description of the technology and clinical care pathway

- Hereditary angioedema (HAE) is a rare genetic disorder characterised by recurrent, unpredictable, painful, and potentially life-threatening episodes of swelling (attacks). It is estimated that between 1 in 50,000 to 1 in 100,000 people in the UK suffer from HAE.[1]

- HAE attacks cause dysfunction and disfigurement and are associated with a wide range of other symptoms depending on the attack location; including pain, vomiting, diarrhea and even asphyxiation.[2,3] The severity and spontaneity of these disabling symptoms mean that patients are incapable or reluctant to perform regular daily activities, which negatively impacts their mental and physical wellbeing.[4]

- Caregivers of HAE patients also experience significant burden due to shared anxiety over attacks, assisting with administration of medications, and assisting patients with their everyday activities.[5] Both patients and caregivers frequently miss work due to HAE attacks, leading to a further societal burden.[5]

- Long-term prophylaxis (LTP) treatments may be prescribed in an attempt to reduce the frequency of attacks in patients with HAE. Current treatments available in England include attenuated androgens, C1-esterase inhibitors (C1-INHs), and lanadelumab.[1]

- Androgens have a well-established history of safety and tolerability concerns associated with long-term use.[6] Hormonal imbalances as a result of androgen treatment can result in a number of undesired side effects. Many patients discontinue or are unsuitable for androgen treatment, and as such are left with no prophylactic treatment option. These patients rely instead on the use of acute therapies on demand, which do not reduce the frequency of attacks, the associated anxiety over their onset, or reduce resource use for the healthcare system.[6]

- Lanadelumab and C1-INHs are only available in England for a very small subset of patients who experience two or more clinically significant attacks per week despite oral prophylactic therapy.[7] Both treatments are injectable therapies, which may not be suitable for all patients.

- There is an urgent need among patients who are currently not well served by available prophylactic treatment options for a therapeutic strategy that is clinically effective, and has proven safety and tolerabilty, whilst also being conveniently administered.

- Berotralstat is an orally administered small molecule inhibitor of plasma kallikrein intended as a long-term prophylaxis treatment for the prevention of acute attacks in patients aged 12 years and older with HAE.

- APeX-2, the pivotal RCT for berotralstat, demonstrated a statistically significant clinical benefit to patients treated with berotralstat, with patients experiencing a 44% reduction in attacks compared with placebo patients. Additionally, 50% of patients receiving berotralstat had a ≥70% reduction in attack rate from baseline.[8] Berotralstat also had a good safety and tolerability profile, with no serious or severe treatment emergent adverse events observed over the trial period.[8]

- The proposed positioning of berotralstat 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.

### *B.1.1 Decision problem*

The submission focuses on part of the technology's marketing authorisation, specifically those adult and adolescent 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.

This is narrower than the marketing authorisation because:

- This position reflects where berotralstat provides the most clinical benefit: patients with the greatest unmet need due to lack of access to effective, well tolerated, long-term preventative therapy. These patients have the most opportunity to benefit in terms of clinical outcomes and improvement in health-related quality of life. This has been ratified by a Delphi panel of UK clinical experts who agreed that this was the appropriate positioning for berotralstat and that this was how it would be used it clinical practice.[9]


 

**Table 1: The decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| **Population** | People aged 12 years and older with hereditary angioedema | Patients aged 12 years and older with HAE who meet the following criteria:<br>• HAE type I or II patients who experience two or more attacks per month who are unsuitable for or refractory to androgens<br>• 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.[9] 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. |
| **Intervention** | BCX7353 | Berotralstat | Berotralstat is the generic name for BCX7353 |

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| **Comparator(s)** | Established clinical management for preventing acute attacks of hereditary angioedema without BCX7353 including but not limited to:<br>• C1-INHs, attenuated androgens and anti-fibrinolytics<br>• Lanadelumab for people eligible for C1-esterase inhibitor treatment in line with NHS England's commissioning policy | 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:<br>• 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. Long-term androgen use is often discontinued due to undesired side effects or lack of efficacy.[6] 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.<br>• Patients are eligible for routine C1-INHs or lanadelumab if they are experiencing two or more clinically |

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| | | | 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.<br><br>• Anti-fibrinolytics such as tranexamic acid are not indicated as long-term prophylactic therapies for patients with HAE.[10] They are instead indicated to be used as a short-term |

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| | | | 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. |

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| **Outcomes** | The outcome measures to be considered include:<br>• frequency of angioedema attacks<br>• severity of angioedema attacks<br>• need for acute treatment<br>• mortality<br>• adverse effects of treatment<br>• health-related quality of life. | The following outcome measure is not included:<br>• Severity of angioedema attacks<br>Additional outcome measures considered include:<br>• Location of attack (specifically differentiating between Laryngeal, Abdominal and Limb/Peripheral attacks)<br>• 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.<br><br>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. |

## *B.1.2 Description of the technology being appraised*

Table 2 presents a brief description of berotralstat for the treatment of HAE. The draft Summary of Product Characteristics (SmPC) can be found in Appendix C.

**Table 2: Technology being appraised**

| | |
|---|---|
| **UK approved name and brand name** | Generic name: berotralstat<br>Brand name: Orladeyo®<br>Alternative identifier: BCX7353 |
| **Mechanism of action** | Plasma kallikrein is a serine protease integral to the contact activation pathway.[12] During contact activation, kallikrein cleaves high-moloecular-weight-kininogen, which in turn produces bradykinin.[13] The activation of the BK B2 receptor by bradykinin results in vasodilatation, increased vascular permeability, and smooth muscle contraction, all of which lead to the tissue swelling that characterizes HAE.[14]<br>Berotralstat is a synthetic small-molecule inhibitor of plasma kallikrein that is an oral treatment for the prevention of attacks in HAE. By inhibiting plasma kallikrein, berotralstat reduces the amount of bradykinin in HAE patients, preventing angioedema attacks.[15] |
| **Marketing authorisation/CE mark status** | 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] |


 

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| **Indications and any restriction(s) as described in the summary of product characteristics (SmPC)** | 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. |
| **Method of administration and dosage** | Berotralstat is an oral therapy. The recommended dose of berotralstat is 150 mg taken once daily.<br>Subjects are instructed to administer the dose at approximately the same time each day with or without food |
| **Additional tests or investigations** | None |
| **List price and average cost of a course of treatment** | The list price of berotralstat is [redacted] for one pack of 28 x 150mg capsules. At the recommended dose of 150 mg per day, this equates to a daily treatment cost of [redacted] and an annual treatment cost of [redacted] per patient.<br>After taking into consideration the effect of the PAS the annual treatment cost will be [redacted] per patient. |
| **Patient access scheme (if applicable)** | A confidential PAS has been submitted and is expected to be approved prior to the first appraisal committee meeting. This arrangement is in the form of a simple PAS at a fixed discounted price [redacted] |

## *B.1.3 Health condition and position of the technology in the treatment pathway*

### B.1.3.1 Overview of hereditary angioedema

HAE is a rare genetic disorder, characterised by recurrent and unpredictable episodes of swelling (attacks). Attacks frequently occur in the extremities, gastrointestinal tract, face or larynx. The effect can range from painful, to acutely disabling, to life-threatening, depending on the site of an attack.[19] HAE is caused by inherited or spontaneous mutations in the contact activation pathway. There are two main subtypes of HAE, Type I and Type II. Type I is due to C1-inhibitor deficiency, accounting for approximately 85% of HAE cases.[20] Type II HAE is the result of C1-inhibitor dysfunction and accounts for approximately 15% of HAE cases.[20] It is estimated that between 1 in 50,000 to 1 in 100,000 people in the UK suffer from HAE.[1]

**Physical symptoms**

HAE attacks are primarily characterised by painful swelling of the skin or mucous membranes.[21] Attacks may be isolated to a single location or across several locations simultaneously, with a number of symptoms that depend on attack location on top of the pain, dysfunction, and disfigurement generally associated with attacks. Swelling within the GI tract can cause symptoms such as nausea, vomiting, diarrhoea and abdominal pain,[2] while laryngeal swelling leads to the obstruction of airways that can result in loss of consciousness or even death due to asphyxiation.[3]

Less common manifestations of HAE include neurologic, pulmonary, renal, urinary, and musculoskeletal symptoms. Neurologic symptoms include headaches, vision disturbances, impaired balance, and disorientation. Pulmonary and oesophageal symptoms include chest pain, shortness of breath and pain whilst swallowing. Urinary symptoms of HAE include urinary retention, bladder spasm, anuria, or pain at micturition. Musculoskeletal symptoms includes pain in the joints, neck, back and arms.[22] Due to the variety and seriousness of symptoms associated with HAE attacks, medical attention is often required during an attack episode. This can be in the form of hospitalisation, A&E visits, ambulance transportation, specialist consultations and more.[23]

The most serious type of HAE attacks are those that affect the larynx due to the associated mortality risk due to asphyxiation, especially in undiagnosed patients. Compared with attacks in other locations, laryngeal attacks are associated with a far greater rate of hospitalisation within intensive care units.[24] Approximately 50% of patients with HAE will experience a serious laryngeal attack within their lifetime.[25]

**Patient burden**

HAE patients experience negative impacts on their mental and emotional wellbeing in addition to physical symptoms. The unpredictable nature of HAE leads to significant anxiety of an imminent attack, with further anxiety caused by the fear of death due to asphyxiation caused by laryngeal swelling. Additionally, the disfiguring symptoms of HAE lead to self-consciousness of personal appearance. These combined effects lead to reluctance to go out into public or perform everyday activities, decreasing patients' quality of life. Both the physical and emotional consequences can also lead to concerns over having children for fear of hereditary transmission.[4]

HAE attacks occur apparently at random but are often triggered by exposure to external stimuli. Commonly reported triggers include emotional stress, physical exertion, and mechanical trauma.[26] This results in a reluctance by patients to participate in certain activities. Participation in sport, exercise, and certain social situations is curtailed, with consequent detrimental effects on both physical and mental health. These restrictions further compound the mental health and physical wellbeing impacts of HAE. The combination of physical symptoms and the impact on mental wellbeing can contribute to significant negative effects on health-related quality of life (HRQoL).

HAE patients struggle to maintain usual levels of functionality and productivity due to the acute physical and emotional reactions experienced during attacks. A study investigating the efficacy of icatibant in clinical practice observed that the median duration of attacks for untreated patients to be 48.0 hours,[27] while the frequency of attacks for patients in the UK has been observed to be 13.5 attacks per year (>1 per month). Patients without adequate preventative treatment can therefore expect to be in a state of attack for approximately 27 days per year.[1] The loss of almost an entire month each year due to attacks can have significant detrimental effects on work or

school productivity. A study into the socioeconomic burden of HAE in European countries discovered that 56% of patients reported missing time from school or work during their most recent attack.[5]

Living with HAE can have far-reaching and devastating consequences for the educational and employment prospects of patients beyond absenteeism. A study performed by HAE international investigating HAE in the UK showed that patients worked fewer hours, had reduced productivity at work, had reduced labour market participation, demonstrated limitations to educational attainment, and missed out on promotions due to HAE that was not properly controlled.[28]

**Caregiver burden**

There is a significant caregiver burden identified for HAE patients.[5] Caregivers offer both physical and emotional support to HAE patients as well as sharing anxiety over attacks.

Physical support comes in the form of actively administering acute therapies during attacks, as well as organising hospital transit and medical appointments. Caregivers often assist patients with daily activities, such as dressing and cooking when the attacks result in temporary disability. Anxiety caused due to the spontaneous nature of attacks is common for caregivers, particularly parents of adolescent HAE patients who are concerned for their child's safety and public embarrassment. Members of the same family or household often suffer with HAE, due to genetic inheritance, which exponentiates the burden of caregivers within the family and levels of shared anxiety.

Caregivers' absenteeism increases alongside the need for patient care, often resulting in a loss of workdays and productivity. A study into the socioeconomic burden of HAE in European countries reported that during episodes of severe attack, 69% of patients reported assistance from carers during their last attack with a mean duration of missed time to be 2.1 days for carers.[5] The study by HAE international showed similar results, with caregivers expected to lose approximately 7 work days per year because of caring for someone with HAE.[28] This study also showed that some caregivers elect not to work due to the requirements of care, and others

reported reduced productivity whilst at work due to the anxiety over the wellbeing of their relative/partner with HAE.[28]

## B.1.3.2 Overview of HAE treatment landscape

**Diagnosis and treatment strategies**

Early diagnosis and effective treatment of HAE is essential to avoid encumbrance due to inappropriate medical care and to reduce the risk of mortality associated with undiagnosed cases.[19] Diagnosis of HAE usually begins with patients displaying recurrent episodes of swelling which last more than 24 hours and are unresponsive to antihistamines, or a history of recurrent unexplained abdominal pain. A family history of similar symptoms can be a strong indicator of angioedema as a hereditary condition. Diagnosis allows for disease specific treatment regimens to be established and significantly reduces the risk of death due to asphyxiation caused by untreated laryngeal swelling.

Treatment of HAE takes the form of three distinct methodologies: treatment of acute attacks, short-term prophylactic (STP) treatments, and LTP treatments. However, eligibility for treatment is dependent on demographics, history of care, and number of attacks in the months prior to evaluation.[29,30] There remains a distinct population of HAE patients in the UK who are ineligible, intolerant, unable or unwilling, to use regular injectable LTP therapies and are without access to effective prophylactic treatment who have substantial unmet need.

**Acute treatments**

The aim of acute treatment is to reduce symptoms of HAE attacks once an attack has already begun. This is achieved through two methods: reducing the severity of the symptoms and reducing the duration of the attack.

Treatments approved in the UK include intravenous C1-INH (e.g. Berinert, Cinryze), recombinant human C1-inhibitor (conestat alpha) or icatibant, a subcutaneous bradykinin-receptor antagonist.[31] Administration of the acute therapies is performed via injection, administered either at a centre of care by a medical professional, or at home if the patient or caregiver has been trained in to deliver therapy.[32] Multiple administrations of different therapies are frequently required for optimal relief of

symptoms, due to the relatively small half-life of the acute therapies and differing levels of patient susceptibility.[31]

Acute therapies do not prevent attacks but instead may help to mitigate the symptoms of an attack when they arise. Patients continue to suffer attacks resulting in significant impacts to their quality of life, increased anxiety as well as having to continue to avoid triggers and adjust their lifestyle accordingly.

**Short-term prophylaxis**

STP treatments are used in the prevention of acute attacks prior to exposure to known triggers.

Minor medical procedures such as dental work or injection of local anaesthetic have been identified as frequently precipitating an attack, and as such STP treatments are often prescribed to mitigate this risk.[29] Major procedures or intubation are also common precursors, or stimuli, for HAE attacks and as such short-term prophylactic therapies are recommended pre-operation to reduce the risk of attack during the procedure. STP treatments may be prescribed when emotional triggers can be pre-empted, for example during student examination periods.

STP treatments typically involve C1-INHs, attenuated androgens or anti-fibrinolytics.[29]

**Long-term prophylaxis**

LTP treatments are used to help prevent acute attacks with the aim of reducing both the physical and psychological implications associated with HAE. Although there is no cure for HAE, patients who experience no attacks have very similar lifestyles to normal healthy people. A Delphi panel of UK clinical experts validated that LTP treatment options are generally considered in patients who experience two or more significant attacks per month or if acute therapies are ineffective or unavailable.[9,29]

There are currently a number of licensed and unlicensed treatments options available in the UK as LTP therapies for patients with HAE, including attenuated androgens, lanadelumab, C1-INHs, and anti-fibrinolytics.[29,33]

**Attenuated androgens**

Attenuated androgens such as danazol are steroid hormones that play a role in the development of male characteristics regulating reproductive activity.[34] Androgens are not licensed for the prevention of acute attacks in HAE patients within the UK, however, they are used in clinical practice as an off-label treatment option for both STP and LTP.

No randomised, double blind, placebo controlled trials have been performed to quantify the clinical efficacy of attenuated androgens in HAE patients and there are well-established safety and tolerability concerns associated with their use. Prolonged use and higher doses are associated with an increased risk of adverse events including weight gain, menstrual irregularities, virilization, headaches, myalgias, depression and anxiety.[6] The adverse events and safety concerns associated with long-term use of androgens mean that their use is associated with high rates of discontinuation.[35]

The safety issues surrounding long-term androgen use has led to recommendations for regular monitoring being introduced. This involves twice yearly liver enzyme, lipid profile, complete blood cell counts and urinalysis and yearly (or twice yearly dependent on dose) spleen ultrasound.[29] These regular monitoring requirements constitute an increased burden for the NHS.

There remains a substantial number of patients who are suitable for prophylaxis but currently have no preventative options for HAE as a result of these adverse events, safety concerns, lack of established clinical efficacy, and the high rates of discontinuation. As such, there remains a large unmet need for a well tolerated, convenient and effective LTP therapy in this patient population.

**C1-esterase inhibitors**

Routine injections of C1-INH (Cinryze) are also used as LTP strategy for eligible HAE patients. The clinical efficacy and safety of Cinryze as a LTP was demonstrated in the CHANGE study.[36]

Under current NHS guidelines the use of routine C1-INHs as long-term prophylactic therapy in HAE patients is commissioned '*for Individuals who fail, or are intolerant of oral prophylaxis and who experience two or more clinically significant attacks per*

*week, despite oral prophylaxis over a period of at least 56 days, requiring treatment with C1-INHs or icatibant'*. Or for '*Individuals in whom oral prophylaxis is contraindicated, for example pregnant women'*.[37]

A very restricted proportion of the UK HAE population receive C1-INHs due to the eligibility criteria for use of C1-INHs as a long-term prophylactic. A UK national audit of HAE performed in 2014 observed that only 8% of 343 patients were receiving C1-INHs as a long-term prophylactic treatment.[1]

Cinryze requires intravenous administration, which entails either administration by a healthcare professional or training to self-administer at home. Intravenous infusions can be very burdensome for patients at the licensed twice a week dosing, which has the potential to result in suboptimal HAE control. In addition, regular and repeated intravenous administration of C1INH can result in the loss of readily accessible veins, resulting in the need for indwelling ports to provide access.[38] The use of indwelling ports also poses a significant risk of thrombosis and infection, as well as the potential physical and psychological discomfort and their use has been discouraged.[29,38] In addition to these considerations some patients may have a fear of needles so regular injectable treatment would not be a suitable option.

Initial administration of C1INH typically occurs at a specialist centre by a medical professional, however subsequent administration requires patients and carers to receive training to be able to administer at home.[39] This introduces further strain on individuals, carers and the health care system to facilitate both the administration of injectable therapies and the training for self-administration. It is therefore clear that there remains an unmet need for patients who have 2 or more HAE attacks per week who are not suitable for IV injectable therapy.

Furthermore, Cinryze is a human plasma-derived product.[36] In recent years there have been significant supply issues associated with plasma derived products, primarily due to a lack of available plasma, since most plasma is derived from human donor plasma collection.[40] Supply is driven by the number of available donors, as well as the number of collections per donor and volume of collection per visit, all of which are factors that cannot be rapidly scaled up in response to demand.[40] There have been occasions where clinical demand has outgrown available supply; recently

this has been exaggerated by the ongoing Covid-19 pandemic.[40] This issue cannot easily be rectified as production cannot increase to fulfil the additional demand.[41] Therefore, there is a risk of future supply issues associated with the availability of Cinryze which would leave HAE patients with limited access to prophylactic treatment.

**Lanadelumab**

Lanadelumab is a subcutaneously administered, monoclonal antibody inhibitor of plasma kallikrein that was approved by NICE in 2019 as a LTP treatment of attacks in HAE patients aged 12 and older. Lanadelumab is recommended as a treatment option only if the patient is eligible for routine C1-INH injections; that is patients having 2 or more clinically significant attacks per week over 8 weeks despite oral preventative therapy.[7]

Clinical efficacy data was based on the HELP-03 RCT which showed a significant reduction in attack rate per four weeks compared against placebo, (0.257 vs 1.967, $p<0.001$).[42] Lanadelumab is administered via subcutaneous injection every 2 weeks, which is associated with a high incidence of injection site reactions (52%)[43], pain (43%)[44] and bruising. Lanadelumab is also associated with development of treatment emergent anti-drug antibodies, the impact of which on the long-term efficacy and safety of lanadelumab is yet to be understood.

There are therefore significant limitations to use of both Cinryze and lanadelumab even for the very limited number of patients eligible for treatment. Whilst the vast majority of patients are reliant on unlicensed therapies that are not clinically proven to be effective.

**Tranexamic acid**

The most commonly used anti-fibrinolytic in HAE patients is tranexamic acid. Tranexamic acid (TXA) is blood clotting agent,[11] and is indicated for STP in HAE patients.[10]

There are efficacy concerns associated with the use of TXA as a preventative therapy in HAE patients. A systematic review on the use of TXA for the treatment of HAE revealed that the evidence base for prophylactic use of TXA is moderate-weak. Although there were several studies demonstrating a beneficial effect of prophylactic

treatment with TXA, the majority of studies were deemed to be low-level evidence and assigned a SIGN grade of 2 or 3.[11] The review identified ten reports (42%) demonstrating that TXA was ineffective or led to worse outcomes following long-term prophylactic treatment in patients with HAE.

TXA in HAE patients is no longer widely recommended or used and as such not considered a relevant comparator to berotralstat. However, given the lack of efficacy data for TXA, there is a great unmet need for the patients who currently receive treatment with it for a treatment option that has been clinically proven to be effective.

### B.1.3.3 Place of berotralstat in the treatment pathway

Berotralstat is an orally administered small molecule inhibitor of plasma kallikrein intended as a LTP treatment for the prevention of acute attacks in adult and adolescent HAE patients aged 12 years and older.

The efficacy of berotralstat was demonstrated in the robust phase 3 randomised control trial, APeX-2, which demonstrated statistically significantly efficacy compared to placebo. The results of APeX-2 showed that berotralstat patients had an overall 44% reduction in attacks compared with placebo patients and 50% of patients receiving berotralstat had a ≥70% reduction in attack rate from baseline compared with 15% of placebo patients [redacted]

Berotralstat also demonstrated a good safety and tolerability profile. Over the course of the study, only one patient receiving 150mg of berotralstat experienced a treatment emergent serious adverse event compared with three placebo patients. Additionally, all study drug related TEAEs were mild to moderate in the 150mg berotralstat group.[8] Berotralstat has no effect on any hormone levels in the body therefore avoiding many of the issues associated with androgen use.

Patients unsuitable or refractory to androgens who experience less than two clinically significant attacks per week, and patients unsuitable for repeated injectable therapies who experience more than two clinically significant attacks per week, are currently forced into a treatment strategy of on-demand use of acute treatment of their HAE attacks. Berotralstat aims to bridge the treatment gap for those patients suitable for prophylaxis for whom androgen treatment is unsuitable or ineffective, as

well as for those patients with 2 or more attacks/week for whom routine injectable C1-INH and lanadelumab are unsuitable. These patients will benefit most from the introduction of berotralstat as a treatment option.

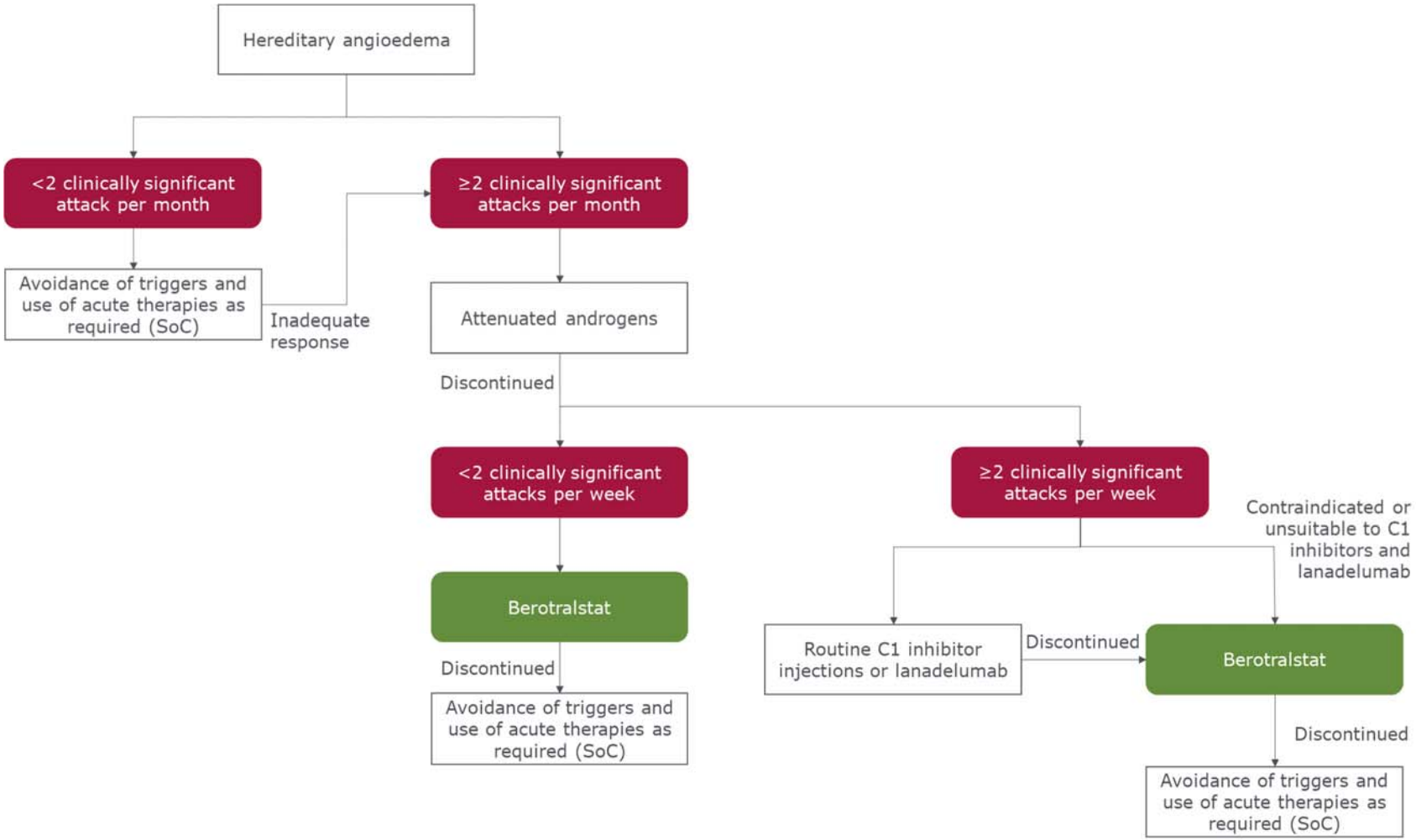
Therefore the patient population with the greatest unmet need that has been identified as the optimal positioning for berotralstat is adult and adolescent patients aged 12 years or older with Type 1 or 2 HAE who:

- Experience ≥2 clinically significant attacks per month and who are unsuitable for and/or refractory to attenuated androgens
- Experience ≥2 clinically significant attacks per week and who are unsuitable for regular injectable prophylaxis with C1-esterase inhibitors or lanadelumab

The intended place of berotralstat in the current treatment pathway is shown in Figure 1.

**Figure 1: HAE treatment pathway flowchart**



### *B.1.4 Equality considerations*

No issues have been identified regarding equality.

## B.2 Clinical effectiveness

**Summary of clinical effectiveness**

- The clinical effectiveness for berotralstat is based on the APeX-2 trial. APeX-2 is a phase III randomised, double-blind, placebo-controlled, parallel group, three-part study to assess the efficacy and safety of berotralstat for the prevention of HAE attacks in patients with Type 1 or 2 HAE. Patients were randomised in a 1:1:1 ratio to receive a once-daily oral dose of either berotralstat 110 mg (n=41), berotralstat 150 mg (n=40), or placebo (N=40). Treatment group 1 (110 mg QD) is not considered clinically relevant to this submission as this dose will not be licensed or marketed in the UK, and no results for this dose will be presented.

- Baseline demographic and disease characteristics were similar across treatment groups and representative of the global HAE patient population.

- APeX-2 demonstrated that berotralstat met the primary efficacy endpoint of reducing the rate of investigator-confirmed HAE attacks compared to placebo in the ITT population. Berotralstat 150 mg statistically significantly reduced the rate of Investigator-confirmed HAE attacks by 44.2% versus placebo [redacted]

- After 24 weeks of treatment with berotralstat 150 mg, [redacted]% of patients experienced a ≥ 50% reduction in attack rate relative to baseline (p=0.005). Ad-hoc analyses demonstrated that 50% of patients treated with berotralstat 150 mg experienced a ≥ 70% reduction in attack rate relative to baseline [redacted] In comparison, 25% and 15% of placebo patients experienced a ≥ 50% and ≥ 70% relative reduction, respectively. The clinical benefit of berotralstat was sustained over time, with no reduction in efficacy observed over the Part 2 extension of APeX-2.

- In every sensitivity analysis performed on the primary efficacy outcome, treatment with berotralstat 150 mg was associated with a statistically significant reduction in investigator confirmed HAE attacks compared to

placebo. This demonstrates the robustness of the study analyses and supports the conclusions of the primary efficacy analysis.

- Berotralstat 150 mg produced statistically significant reductions in HAE attack rate compared to placebo in [redacted] This demonstrates that berotralstat 150 mg is effective in preventing HAE attacks in a wide variety of patients.

- Treatment with berotralstat 150 mg was well-tolerated in the study. No patients who received berotralstat 150 mg experienced a SAE or drug-related Grade 3 or 4 TEAE, while one patient in the placebo arm experienced a SAE. Discontinuation due to a TEAE was experienced by one patient in each of the berotralstat 150 mg and placebo arms.

### *B.2.1 Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify relevant literature regarding the efficacy and safety of treatments for HAE. Full details of the methodology and results of the SLR are detailed in Appendix D.

### *B.2.2 List of relevant clinical effectiveness evidence*

The efficacy and safety of berotralstat (Orladeyo®) has been evaluated in APeX-2 (NCT03485911), a phase III randomised, double-blind, placebo-controlled, parallel group study. The study evaluated berotralstat at two dose levels (110mg and 150mg) for the prevention of attacks in patients with hereditary angioedema. The clinical data and cost-effectiveness analyses presented in this submission are based on this study. Treatment group 1 (110 mg QD) is not considered clinically relevant to this submission as this dose will not be licensed or marketed in the UK, and no results for this dose will be presented. Table 3 details the clinical effectiveness evidence from APeX-2 that is relevant to this submission.

**Table 3: Clinical effectiveness evidence**

<table>
<tr><td>Study</td><td colspan="5">APeX-2 (NCT03485911)</td></tr>
<tr><td>Study design</td><td colspan="5">Phase III randomised, double-blind, placebo-controlled multi-centre, three-part trial</td></tr>
<tr><td>Population</td><td colspan="5">Adults and adolescents (≥12 years of age) with Type 1 or Type 2 HAE</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">110 mg berotralstat (N=41) or 150mg berotralstat (N=40) administered orally once daily for 24 weeks</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Placebo (N=40) administered orally once daily for 24 weeks</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>x</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>x</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">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.</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• Frequency of angioedema attacks<br>• Severity of angioedema attacks<br>• Need for acute treatment<br>• Mortality<br>• Adverse effects of treatment<br>• Health-related quality of life</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Location of attack<br>• Duration of attacks</td></tr>
</table>

## *B.2.3 Summary of methodology of the relevant clinical effectiveness evidence*

### B.2.3.1 Trial design

APeX-2 was a global (11 countries, 40 clinical sites), randomised, double-blind, multi-centre, placebo-controlled, parallel group, three-part phase III trial in patients with HAE.

The primary objective of Part 1 of the study was to determine the efficacy of prophylactic berotralstat 110 and 150 mg administered orally QD for 24 weeks (the 'Part 1' time period) compared to placebo in patients with HAE. The primary efficacy

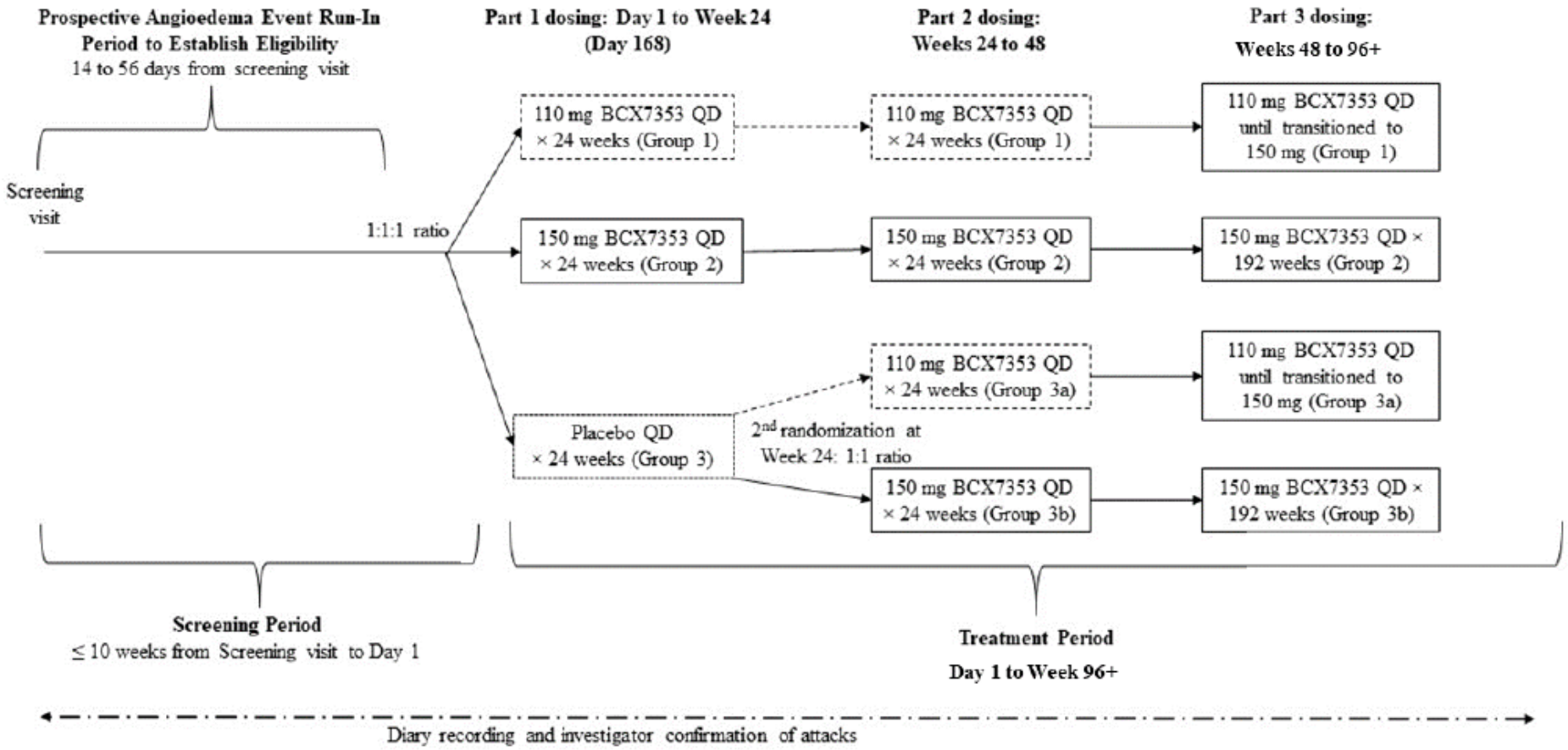
endpoint (the rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period) was assessed after the last patient completed Part 1.

Part 2 and Part 3 gathered further long-term data on the efficacy and safety of berotralstat. In Part 2, all patients received active treatment with berotralstat from Weeks 24 through 48, albeit blinded to dose. Part 3 of the study was an open-label extension to APeX-2 that provided access to berotralstat if appropriate.

The study schematic of APeX-2 can be found in Figure 2.

**Figure 2: APeX-2 Study Schematic**




Source: APeX-2 CSR[45]
Abbreviations: BCX7353, berotralstat; QD, once daily

**APeX-2 study - Part 1**

Subjects with HAE were eligible for the study following screening, which included demonstration of a minimum number of qualifying attacks during a prospective run-in period of 14 to 56 days from the date of screening.

Patients in Part 1 of the study were randomised in a 1:1:1 ratio into one of three treatment groups:

- Group 1 (n = 41): Berotralstat 110 mg administered orally QD for 24 weeks
- Group 2 (n = 40): Berotralstat 150 mg administered orally QD for 24 weeks
- Group 3 (n = 40): Placebo administered orally QD for 24 weeks

Enrolment into treatment groups was stratified by the HAE attack rate over the period from screening to randomisation (≥ 2 attacks per month vs. < 2 attacks per month). The main study comprised adult patients (aged ≥ 18 years of age); with a sub-study in participating regions comprising adolescent patients (12 to 17 years of age). Main study and sub-study patients were randomised via a separate randomisation scheme; however, study-mandated procedures were identical, and the analyses presented in this submission included all patients who participated in the study.

**APeX-2 study - Part 2**

Part 2 of the study began at the end of the Week 24. Subjects in Groups 1 and 2 (110 and 150 mg QD berotralstat, respectively) continued to receive the same blinded berotralstat dose to which they were randomised in Part 1 of the study. Subjects who had been randomised to Group 3 (placebo) in Part 1 of the study underwent a second randomisation in a 1:1 ratio to receive either a 110- or 150-mg blinded dose beginning at the Week 24 visit (see Figure 2). The active dose strength a patient received in Part 2 was blinded for all patients and assessors, however patients were informed at the pre-trial screening visit that they were to receive an active dose of berotralstat in Part 2.

**APeX-2 study - Part 3**

Subjects entered Part 3 at the Week 48 visit, where they received their Part 2 dose of berotralstat as unblinded drug.

**Eligibility criteria**

The study was limited to adults and adolescents (≥ 12 years of age) of both sexes with HAE Type 1 or Type 2. The patient must have had ≥ 2 HAE attacks that met all the requirements below during the run-in period of a maximum of 56 days from the screening visit:

- The attacks were unique, which was defined as an attack that did not begin within 48 hours of the end of a previous attack.
- The attacks must have either been treated, required medical attention, or been recorded as causing functional impairment based on patient entry in the e-diary.
- The attacks included symptoms of swelling.
- The attacks were confirmed by the investigator to be HAE attacks.

Additional details regarding the inclusion and exclusion criteria of patients entering the APeX-2 trial are presented in Table 4.

**Table 4: APeX-2 inclusion and exclusion criteria**

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Males and non-pregnant, non-lactating females ≥ 18 years of age (main study) or ≥ 12 to 17 years of age (sub-study).<br>• Able to provide written, informed consent. Subjects who were 12 to 17 years of age at screening for the sub-study had to be able to read, understand, and be willing to sign an assent form in addition to a caregiver providing informed consent.<br>• Subject weight of ≥ 40 kg.<br>• A clinical diagnosis of hereditary angioedema Type 1 or Type 2. | • Any clinically significant medical or psychiatric condition or medical history that, in the opinion of the investigator or sponsor, would interfere with the patient's ability to participate in the study or increased the risk to the patient by participating in the study.<br>• Dementia, altered mental status, any psychiatric condition, or stay in an institution further to an official or court order that would prohibit the understanding or rendering of informed consent or participation in the study. |

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Access to and ability to use 1 or more SOC-Rx approved by the relevant competent authority for the treatment of acute attacks of HAE (icatibant, plasma-derived C1-INH, ecallantide, or recombinant C1-INH). Cinryze used for acute treatment of HAE attacks was an acceptable medication for this purpose.<br>• Subjects must have been medically appropriate for on-demand treatment as the sole medicinal management for their HAE during the study.<br>• Female patients had to either:<br>o Be a woman of childbearing potential who agreed to use at least an acceptable effective contraception method during the study and for a duration of 30 days after the last dose of study drug.<br>o Be a woman declaring herself as either sexually abstinent or exclusively having female sexual partners.<br>• Male patients were required to comply with the following requirements through the end of the study:<br>o Subjects with female partners of a childbearing potential had to agree to utilise at least one acceptably effective contraception method<br>• The patient must have had ≥ 2 HAE attacks that met all the requirements | • Anticipated use of short-term prophylaxis of angioedema attacks for a pre-planned procedure during the screening or study periods.<br>• Concurrent diagnosis of any other type of recurrent angioedema.<br>• Clinically significant abnormal electrocardiogram (ECG) at the screening visit.<br>• Any clinically significant history of angina, myocardial infarction, syncope, clinically significant cardiac arrhythmias, left ventricular hypertrophy, cardiomyopathy, or any other clinically significant cardiovascular abnormality such as poorly controlled hypertension.<br>• Known family history of sudden cardiac death.<br>• History of or current implanted defibrillator or pacemaker.<br>• Any abnormal laboratory or urinalysis parameter at screening that, in the opinion of the investigator, was clinically significant and relevant for this study.<br>• Prior enrolment in a berotralstat study.<br>• Suspected C1-INH resistance in the opinion of the investigator or sponsor.<br>• History of alcohol or drug abuse within the previous year prior to the screening visit or current evidence of substance dependence or abuse<br>• Use of androgens or tranexamic acid for prophylaxis of HAE attacks within the 28 days prior to the screening visit or initiation during the study.<br>• Use of C1-INH for prophylaxis of HAE attacks within the 14 days prior to the screening visit or initiation during the study.<br>• Use of excluded medications.<br>• Use of an angiotensin-converting enzyme inhibitor within 7 days of the baseline visit or planned initiation during the study. |

| Inclusion criteria | Exclusion criteria |
|---|---|
| | • Initiation of an oestrogen-containing hormonal contraceptive within 56 days of the screening visit or planned initiation during the study.<br>• Current participation in any other investigational drug study or having received another investigational drug within 30 days of the screening visit. |

Source: APeX-2 CSR[45]
Abbreviations: C1-INH, C1 esterase inhibitor; ECG, electrocardiogram; HAE, hereditary angioedema; SOC-Rx, standard of care acute attack medication.

### Setting and location

Patients were enrolled from 40 sites in 11 countries including the United States, Austria, Canada, Czechia, France, Germany, Hungary, North Macedonia, Romania, Spain and the United Kingdom.

### Interventions

Subjects were instructed to take [redacted] capsules orally QD at approximately the same time each day with whichever meal was typically the largest meal of the day, or up to 30 minutes after consuming that meal, through the end of Part 1 as follows:

- Treatment Group 1 (110 mg berotralstat) QD), N=41
  - Part 1: [redacted]mg capsules of berotralstat QD × 24 weeks
  - Note: Treatment group 1 (110 mg QD) is not considered clinically relevant to this submission.
- Treatment Group 2 (150 mg berotralstat QD), N=40
  - Part 1: [redacted]mg capsules of berotralstat QD × 24 weeks
  - Note: All cost-effectiveness analyses in this submission will use data relevant to treatment group 2 (150mg berotralstat), as this is the dose under assessment by the EMA.[16]
- Treatment Group 3, N=40
  - Part 1: [redacted] capsules of placebo QD × 24 weeks

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.

Participation in the study was strictly voluntary; a patient may have withdrawn consent to contribute additional study information at any point. A patient who withdrew consent was requested to attend an early termination visit to complete all end-of-study evaluations.

**Outcomes**

The primary efficacy endpoint was the rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period (Part 1).

The following secondary endpoints were assessed:

- Change from baseline in Angioedema Quality of Life Questionnaire (AE-QoL) total score at Week 24.
    - AE-QoL scores range from 0 to 100, with a decrease indicating an improvement in the patient's QoL. The minimal clinically important difference (MCID) for the AE-QoL questionnaire is -6 (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

Safety outcomes evaluated included the following:

- Treatment-emergent adverse events (TEAEs)
- Discontinuation due to TEAEs
- Treatment emergent serious adverse events (SAEs)
- Grade 3 or Grade 4 TEAEs

### B.2.3.2 Summary of trial design

A summary of the trial design for APeX-2 can be found below in Table 5.

**Table 5: APeX-2 Study Methodology**

| | |
|---|---|
| Trial number | NCT03485911 (APeX-2) |
| Trial Design | Phase III randomised, double-blind, placebo-controlled, parallel group, three-part study |
| Eligibility criteria for participants | **Key inclusion criteria**<br>• Males and non-pregnant, non-lactating females ≥ 12 years of age.<br>• Subject weight of ≥ 40 kg. |

| | |
|---|---|
| | • A confirmed diagnosis of Type 1 or 2 HAE.<br>• The patient must have had ≥ 2 HAE attacks that met all of the requirements below during the run-in period of a maximum of 56 days from the screening visit:<br>1. The attacks were unique.<br>2. The attacks must have either been treated, required medical attention or been documented to cause functional impairment based on patient entry in the e-diary.<br>3. The attacks included symptoms of swelling.<br>4. The attacks were confirmed by the investigator to be HAE attacks. |
| Settings and locations | 40 sites in 11 countries including the UK |
| Trial drugs | **Intervention:** 110mg (N=41) or 150mg (N=40) QD<br>**Comparator:** Placebo (N=40) administered orally QD |
| Permitted and disallowed concomitant medication | [redacted] |

| | |
|---|---|
| | [redacted] |
| Primary efficacy outcomes | • The primary efficacy endpoint was the rate of investigator-confirmed HAE attacks during dosing in the entire 24-week treatment period |
| Secondary efficacy outcomes | • Change from baseline in Angioedema Quality of Life Questionnaire (AE-QoL) total score at Week 24<br>• Number and proportion of days with angioedema symptoms through 24 weeks<br>• Rate of investigator confirmed HAE attacks during dosing in the effective treatment period |
| Exploratory endpoints | • The proportion of responders to study drug, defined as ≥50%, ≥70%, and ≥90% relative reduction in the rate of investigator confirmed HAE attacks during treatment, compared with the baseline attack rate<br>• Rate of attacks treated with HAE attack medications over 24 weeks<br>• Amount of HAE attack medications used over 24 weeks<br>• Number and proportion of patients with no attacks over 24 weeks<br>• Number of attack-free months over 24 weeks<br>• Attack characteristics: rate of attacks at anatomical locations, patient-reported severity of attacks, duration of attacks, symptoms of attacks, triggers of attacks, care sought for attacks, and impact of attacks on appearance and daily activities |
| Safety outcomes | • Number and proportion of patients with TEAE<br>• Number and proportion of patients who discontinue due to a TEAE<br>• Number and proportion of patients who experience a treatment-emergent SAE<br>• Number and proportion of patients who experience a Grade 3 or Grade 4 TEAE<br>• Number and proportion of patients who experience a treatment-emergent Grade 3 or Grade 4 laboratory abnormality |
| Pre-planned subgroups | Subgroup analyses for the primary endpoint of investigator-confirmed attack rate during the entire 24-week dosing period and the secondary endpoint of Week 24 change from baseline AE-QoL (total score) was provided by:<br>[redacted]<br>• [redacted]<br>• [redacted] |

Abbreviations: AE, adverse event; HAE, hereditary angioedema; QD, once daily; QoL, quality of life; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UK, United Kingdom

### B.2.3.3 Trial population

**Subject disposition**

A total of 160 patients were screened, 121 patients were randomised (ITT population), and 120 of these patients (99%) were treated (safety population). Of the [redacted] screen failures who were not enrolled in the study, [redacted] patients either did not meet one or more inclusion criteria or did meet one or more exclusion criteria, and three patients withdrew consent.

The disposition of patients within the trial is shown in Figure 3**: APeX-2 Study Disposition**

.

**Figure 3: APeX-2 Study Disposition**

[redacted]

Source: APeX-2 CSR[45]
Abbreviations: ITT, intent to treat, N/n, number of patients

**Baseline characteristics**

A total of 121 patients were included in the ITT population, which were randomised in a 1:1:1 ratio into one of three treatment groups: 110 mg berotralstat once daily (n=41), 150mg berotralstat once daily (n=40) and placebo once daily (n=40).

Baseline demographic characteristics were representative of the HAE patient population and similar across treatment groups, although patients in the berotralstat 150 mg group had a higher median weight (82 kg) vs. patients in the placebo group (77 kg). 66% of patients were female and the mean age was 41.6 years, including 6 adolescent patients 12 to 17 years of age enrolled at sites in the United States (US) and 9 elderly patients 65 to 74 years of age enrolled globally. More female patients enrolled vs. male patients as was expected based on previous clinical studies in HAE.

The patient population was also representative of the typical HAE patient characteristics in terms of age of HAE symptom onset (mean age of 11 years), age of HAE diagnosis (mean age of 20 years), and positive family history of HAE.[46]

**Table 6: APeX-2 Baseline Characteristics**

| | **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] |
| Adult | [redacted] | [redacted] |
| 18-64 years | [redacted] | [redacted] |

| | Berotralstat 150mg QD | Placebo QD |
|---|---|---|
| ≥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%) |

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.

Source: APeX-2 CSR[45]
Abbreviations: BMI, body mass index; CDC, Center for Disease Control and Prevention; eCRF, electronic case report form; HAE, hereditary angioedema; ITT, intent to treat; N, number of patients; n, number of patients in the subgroup.

### *B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

Populations for analysis were defined as follows:

- Safety population: The safety population included all patients who received [redacted] of study treatment. This population was used in the assessment and reporting of demographic information, berotralstat drug concentrations, accountability, baseline disease characteristics, and safety data.

- Intent to Treat population (ITT): The ITT population included all randomised patients, regardless of whether study treatment was administered. This population was the primary population for the analysis of the efficacy and health outcomes data.

[redacted]

Table 7 shows a summary of the statistical analysis plan (SAP) for the trial.

**Table 7: APeX-2 Summary of statistical analyses**

| | **APeX-2** |
|---|---|
| **Hypothesis objective** | The primary objective was to determine the efficacy of prophylactic berotralstat (BCX7353) 110 and 150 mg administered QD for 24 weeks compared to placebo in patients with HAE. |
| **Statistical analysis** | Treatment comparisons between each berotralstat dose and placebo in the rate of investigator confirmed HAE attacks during the Part 1 (week 1 to week 24) dosing period were analysed using both a Poisson regression model and a negative binomial model. The number of investigator-confirmed attacks was included as the dependent variable, the treatment was included as a fixed effect, the stratification variable (baseline attack rate) was included as a covariate, and the logarithm of duration on treatment was included as an offset variable. The estimated attack rate for each treatment group, the treatment differences expressed as the attack rate ratio (berotralstat over placebo rate ratio), and the associated 95% confidence intervals (CIs) were provided from the Poisson regression model and the negative binomial model. The Poisson model assumed that the mean and variance are equal. When the variance in the data was larger than the mean, the model was said to be over-dispersed. To examine the appropriateness of the Poisson model, the same data was analysed using a negative binomial model and its dispersion parameter was evaluated. As the dispersion parameter from the negative binomial model was significant for the primary analysis, results from the negative binomial model were used throughout this report. |

| | |
|---|---|
| | The attack rate used in the Part 1 primary analysis was based on the observed data until the time of dosing in Part 2 or the time of treatment discontinuation, whichever was earlier. For the primary analysis, 3 missing data sensitivity analyses were conducted for handling of data for patients who discontinued study treatment prior to the end of Part 1: use of post-treatment discontinuation data without imputation, use of post-treatment discontinuation data with imputation, and a tipping point analysis on post-treatment discontinuation data with imputation. |
| **Sample size, power calculation** | Assuming a normalised placebo attack rate of 1 unit and a common standard deviation (SD) of ± 0.55 attacks/week for berotralstat and placebo attack rates, a sample size of 32 patients had a 94% power to detect a 50% attack rate reduction (a treatment difference of 0.5 attacks/week) between berotralstat and placebo, based on a 2-sided test at significance level of 0.05. [redacted] |
| **Data management, patient withdrawals** | [redacted] A total of 108 (90%) of the 120 treated patients completed study drug dosing in Part 1: 37 berotralstat 110 mg patients (90%), 37 berotralstat 150 mg patients (93%), and 34 placebo patients (87%). All 108 patients who completed study drug dosing in Part 1 continued on to Part 2. |

Abbreviations: CIs, confidence intervals; HAE, hereditary angioedema; QD, once daily; SD, standard deviation

## *B.2.5 Quality assessment of the relevant clinical effectiveness evidence*

A complete quality assessment for APeX-2 is provided in Appendix D.

## *B.2.6 Clinical effectiveness results of the relevant trials*

### B.2.6.1 Primary efficacy endpoint: Rate of investigator confirmed HAE attacks

#### Part 1 results

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.

Table 8 shows the results of the primary efficacy endpoint for berotralstat and placebo.

**Table 8: Summary of Investigator-confirmed attack rates (ITT Population)**

| Primary Endpoint | Berotralstat 150mg; N=40 | | | Placebo; N=40 |
|---|---|---|---|---|
| | Rate per 28 days | Active vs Placebo % (95% CI) | P-value | Rate per 28 days |
| Investigator-confirmed attack rate[a] | 1.31 | -44.2% (-59.5, -23.0) | < 0.001 | 2.35 |
| 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[45]
Abbreviations: ITT, intent to treat; N, number of patients; vs, versus

### Investigator confirmed-attack rates over time (Part 1)

The reductions in HAE attack rate occurred over the first month of treatment and were sustained for the remaining 5 months of Part 1. 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.

Figure 4**: Plot of Mean Investigator-confirmed Attack Rate by Month (ITT Population)**

demonstrates the difference in mean investigator-confirmed attacks by month for each treatment arm.

**Figure 4: Plot of Mean Investigator-confirmed Attack Rate by Month (ITT Population)**

Source: APeX-2 CSR[45]
Abbreviations: ITT, intent to treat; N, number of patients

**Table 9: Summary of Rate of Investigator-confirmed Attacks by Month (ITT Population)**

| Visit Attack Rate | Observed | | Change from Baseline | |
|---|---|---|---|---|
| | Berotralstat 150 mg (N=40) | Placebo (N=40) | Berotralstat 150 mg (N=40) | Placebo (N=40) |
| Baseline attack rate[a] | | | | |
| N | [redacted] | [redacted] | - | - |
| Mean (SD) | [redacted] | [redacted] | - | - |
| Median | [redacted] | [redacted] | - | - |
| Range | [redacted] | [redacted] | - | - |
| Month 1 attack rate[a] | | | | |
| N | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] | [redacted] |
| Range | [redacted] | [redacted] | [redacted] | [redacted] |
| Month 2 attack rate[a] | | | | |
| N | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] | [redacted] |
| Range | [redacted] | [redacted] | [redacted] | [redacted] |
| Month 3 attack rate[a] | | | | |
| N | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] | [redacted] |
| Range | [redacted] | [redacted] | [redacted] | [redacted] |
| Month 4 attack rate[a] | | | | |
| N | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] | [redacted] |
| Range | [redacted] | [redacted] | [redacted] | [redacted] |
| Month 5 attack rate[a] | | | | |
| N | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] | [redacted] |
| Range | [redacted] | [redacted] | [redacted] | [redacted] |
| Month 6 attack rate[a] | | | | |
| N | [redacted] | [redacted] | [redacted] | [redacted] |

| | | | | |
|---|---|---|---|---|
| Mean (SD) | [redacted] | [redacted] | [redacted] | [redacted] |
| Median | [redacted] | [redacted] | [redacted] | [redacted] |
| Range | [redacted] | [redacted] | [redacted] | [redacted] |
| Notes: [a] Monthly attack rate was defined as the total number of investigator-confirmed HAE attacks experienced during the treatment period adjusted for the length of a month (defined as 28 days) and the number of days the patient was on treatment during that month. | | | | |

Source: APeX-2 CSR[45]
Abbreviations: N, number of patients; SD, standard deviation

### B.2.6.2 Sensitivity analyses

Six sensitivity analyses (SAs) were performed for the primary analysis which are described below:

[redacted]

All six sensitivity analyses were supportive of the robustness of the primary analysis outcomes. Results for the SAs 1-5 are presented below in

**Figure 5: Forest Plot of Results of Sensitivity Analyses of Investigator-confirmed Attack Rate for Entire Dosing Period and Effective Dosing Period**

and

**Table *10***. No results are presented for SA 6. [redacted]

**Figure 5: Forest Plot of Results of Sensitivity Analyses of Investigator-confirmed Attack Rate for Entire Dosing Period and Effective Dosing Period**

Berc [redacted] 4]

**Table 10: Results of the Sensitivity Analyses**

| Investigator-confirmed attack rate[a] | Berotralstat 150mg | | | | Placebo | |
|---|---|---|---|---|---|---|
| | N | Rate per 28 days[b] | Active vs Placebo % (95% CI) | P-value | N | Rate per 28 days[b] |
| SA1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SA2 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SA3 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SA4 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SA5 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SA6 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

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).[b] Statistical analysis was based on a negative binomial regression model. The number of investigator-confirmed attacks was included as the dependent variable, the treatment was included as a fixed effect, baseline investigator-confirmed attack rate was included as a covariate, and the logarithm of duration on treatment was included as an offset variable.

Source: APeX-2 CSR[45]
Abbreviations: N, number of patients; SA, sensitivity analysis; vs, versus

**Part 2**

Part 2 of APeX-2 began at the end of the week 24 visit and finished at the end of week 48. The reduction in mean attack rate [redacted]. This is displayed in Figure 6**: Mean Investigator-confirmed Attack Rate by Month, Patients Completing 48 Weeks of Dosing**. In patients completing 48 weeks of dosing, mean (SD) HAE attack rates [redacted] attacks per month at baseline

to [redacted] attacks per month at month 6, and [redacted] attacks per month at month 12.[47]

**Figure 6: Mean Investigator-confirmed Attack Rate by Month, Patients Completing 48 Weeks of Dosing**

Source: Aygören-Pürsün et al. 2020[47]
Abbreviations: BL, baseline; n, number of subjects; SEM, standard error of the mean

In subjects 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 150mg (

Figure *7*: **Mean Investigator-confirmed Attack Rate by Treatment Group, Patients Completing 48 Weeks of Dosing**

).

**Figure 7: Mean Investigator-confirmed Attack Rate by Treatment Group, Patients Completing 48 Weeks of Dosing**

Source: Wedner et al. 2020[48]
Abbreviations: BL, baseline; N, number of subjects; SEM, standard error of the mean

## B.2.6.3 Secondary efficacy endpoints

### Angioedema Quality of Life Questionnaire (AE-QoL) total score – Part 1

The AE-QoL questionnaire scores indicated that patients treated with berotralstat 150 mg had greater improvements in QoL than those treated with placebo, and had an average improvement in AE-QoL score that exceeded the MCID. 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.

**Table 11: Summary of AE-QoL Scores at Week 24 (ITT Population)**

| | Change from Baseline | |
|---|---|---|
| | **Berotralstat 150mg; N=40** | **Placebo N=40** |
| N | [redacted] | [redacted] |
| AE-QoL total score | | |
| LSM | [redacted] | [redacted] |
| Standard error | [redacted] | [redacted] |
| LSM difference from placebo | [redacted] | [redacted] |
| 95% CI | [redacted] | [redacted] |
| P-Value | [redacted] | [redacted] |

Source: APeX-2 CSR[45]
Abbreviations: AE-QoL, Angioedema Quality of Life; CI, confidence interval; ITT, intent to treat; LSM, least squares mean; N, number of patients

**Angioedema Quality of Life Questionnaire (AE-QoL) total score – Part 2**

Whereas assessment of quality of life was a secondary objective in Part 1, it was a primary objective in Part 2. Improvements in the mean change from baseline AE-QoL total score exceeding MCID=6 were sustained throughout the 48 weeks. At week 48, the mean (SD) change from baseline in AE-QoL total score was [redacted] as shown in Figure 8**: Mean Change from Baseline in Total AE-QoL Score Over Time Through Week 48 with Berotralstat 150mg**

. Additionally, 77% of patients had reductions AE-QoL total score that exceeded the MCID at 48 weeks.[49]

**Figure 8: Mean Change from Baseline in Total AE-QoL Score Over Time Through Week 48 with Berotralstat 150mg**

[redacted]

Source: Johnston et al. 2020[49]
Abbreviations: AE-QoL, Angioedema Quality of Life; ITT, intent to treat; N, number of patients; SEM, standard error of the mean

### Number and proportion of days with angioedema symptoms through 24 weeks

The analysis demonstrated that 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.

### Rate of investigator confirmed HAE attacks during dosing in the effective treatment period

Results demonstrate that 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 12: Rate of Investigator-confirmed Attacks During Effective Treatment Period (ITT Population)**

| **Attack Rate During Effective Treatment Period** | **Berotralstat 150mg; N=40** | **Placebo N=40** |
|---|---|---|
| Investigator-confirmed attack rate[7] | | |
| N | 40 | 39 |
| Mean (SD) | [redacted] | [redacted] |

| | | |
|---|---|---|
| Median | [redacted] | [redacted] |
| Range | [redacted] | [redacted] |
| Negative binomial regression analysis[6] | | |
| 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% | |

Source: APeX-2 CSR[45]
Abbreviations: CI, confidence interval; ITT, intent to treat; N, number of patients; SD, standard deviation

### B.2.6.4 Exploratory endpoints

#### Responder analysis

Treatment with berotralstat QD for 24 weeks was associated with a ≥ 50% reduction in attack rate relative to baseline in [redacted]% (p=0.005) of patients. In ad-hoc analyses, 50% [redacted] of patients treated with berotralstat 150 mg experienced a ≥ 70% reduction in attack rate relative to baseline. In comparison, 25% and 15% of placebo patients experienced a ≥ 50% and ≥ 70% relative reduction in attack rate from baseline, respectively. These statistically significant results indicate that patients had clinically meaningful responses to berotralstat. These results are included in the continuation rule in the cost-effectiveness economic model.

#### Use of HAE SOC-Rx

Subjects chose to treat fewer attacks with HAE SOC-Rx when using berotralstat 150 mg, reducing the rate of HAE attacks that patients treated by 49% [redacted] compared with placebo. This different was larger than the observed reduction in attack rate. The use of berotralstat will substantially reduce the burden on the NHS for HAE treatment through the reduction of attacks that require acute treatment.

#### Location of attack

Berotralstat 150 mg reduced the HAE attack rate at all locations, including peripheral-only attacks and the potentially life-threatening laryngeal attacks.

Berotralstat reduced peripheral-only attacks by [redacted] An ad-hoc analysis of laryngeal attacks showed that treatment with berotralstat reduced laryngeal attacks by [redacted] compared to placebo.

**Duration of attack – Part 1**

The mean (SD) duration of HAE attacks for berotralstat were [redacted] hours, compared with [redacted] in the placebo group. Attack durations according to locations are specified below in Table 13.

**Table 13: Attack-level Duration of Investigator-confirmed Attacks (ITT population)**

| Duration from start of the attack to the end of the attack (hours)[b] | Berotralstat 150 mg (N=40) | Placebo (N=40) |
|---|---|---|
| All attacks[a] | | |
| N | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] |
| Median | [redacted] | [redacted] |
| Range | [redacted] | [redacted] |
| Abdominal-only attacks[a] | | |
| N | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] |
| Median | [redacted] | [redacted] |
| Range | [redacted] | [redacted] |
| Peripheral-only attacks[a] | | |
| N | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] |
| Median | [redacted] | [redacted] |
| Range | [redacted] | [redacted] |
| Mixed-location attacks[a] | | |
| N | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] |
| Median | [redacted] | [redacted] |
| Range | [redacted] | [redacted] |
| Notes: [a] Duration of each confirmed attack was calculated in hours, based on the start and stop date and time of the reported attack. For investigator-confirmed attacks comprised of 2 or more patient-reported attacks, the | | |

duration was calculated from the start date and time of the first attack to the stop date and time of the last attack. [b] Duration of each confirmed attack was calculated in hours, based on the start and worst over date and time of the reported attack. For investigator-confirmed attacks comprised of 2 or more patient-reported attacks, the duration was calculated from the start date and time of the first attack to the worst over date of the last attack.

Source: APeX-2 CSR[45]
Abbreviations: N, number of patients; SD, standard deviation

## Duration of attack – Part 2

[redacted]

**Table 14: Efficacy Results for Subjects on Placebo in Part 1 and Re-Randomized to Berotralstat in Part 2**

| Variable, mean (SD) | Part 1<br>Placebo | Part 2<br>150mg after placebo |
|---|---|---|
| Duration of attack, hours* | [redacted] | [redacted] |
| Days with angioedema symptoms | [redacted] | [redacted] |

*Ad-hoc analysis

Source: Wedner et al. 2020[48]

Abbreviations: SD, standard deviation

### EuroQol 5-Dimensional 5-Level Questionnaire Scores

EuroQol 5-Dimensional 5-Level (EQ-5D-5L) Visual Analogue Scale (VAS) and Index scores were collected at baseline and every 4 weeks thereafter in APeX-2.

There are a number of limitations with the use of the EQ-5D-5L to characterise HRQoL in patients with HAE, which may mean it is unsuitable for this purpose.

Due to the randomness of HAE attacks, it would have been unlikely for attacks to coincide with the timing of EQ-5D-5L collection. Patients were asked to report their HRQoL based on recall. This use of recalled EQ-5D-5L is not a validated way of using the measure and so should be considered as experimental or 'beta' data. It is not clear whether patients recalled their HRQoL accurately, or what factors may have biased this recall. There is also a small chance that EQ-5D-5L administration would have coincided with when patient's experienced HAE attacks. As such, EQ-

5D-5L data from the trial cannot be used to calculate reliable estimates of attack-free utilities.

EQ-5D-5L is a generic measure associated with considerable uncertainty or variability and can be insensitive to specific disease characteristics, further limiting it's appropriateness in HAE.

[redacted]

Figure 9 shows the EQ-5D-5L results for berotralstat and placebo over the APeX-2 study period.

**Figure 9: EQ-5D-5L VAS and Index results**

## *B.2.7 Subgroup analysis*

Prespecified subgroup analyses of the primary efficacy endpoint were performed for

[redacted]

While there were some differences in response within a subgroup category,

[redacted]

Notable decreases in the rate of Investigator-confirmed attacks include the ≥ 2 attacks/month subgroup, which experienced an attack rate reduction of [redacted] versus placebo [redacted] and 'Yes' to prior androgen use with a rate of [redacted] versus placebo [redacted]

Further results are presented Figure 10**: Forest Plots of Results of Subgroup Analyses of Investigator-confirmed Attack Rate for Entire Dosing Period, Percent Rate Reduction from Placebo (ITT Population; Includes Ad-hoc Subgroups)**

and Table 15.

**Figure 10: Forest Plots of Results of Subgroup Analyses of Investigator-confirmed Attack Rate for Entire Dosing Period, Percent Rate Reduction from Placebo (ITT Population; Includes Ad-hoc Subgroups)**

Source: APeX-2 CSR[45]
Abbreviations: BCX7353, berotralstat; BMI, body mass index; CI, confidence interval; eCRF, electronic case report form; HAE, hereditary angioedema; ITT, intent to treat; SAP, Statistical Analysis Plan.

The subgroup analyses support the consistency of berotralstat efficacy in reducing the rate of HAE attacks.

**Table 15: Summary of Investigator-confirmed Attack Rates by Subgroups (ITT Population; With Ad-hoc Subgroups)**

| Subgroup Investigator-confirmed attack rate[a] | Berotralstat 150 mg; n=40 | | | | Placebo n=40 | |
|---|---|---|---|---|---|---|
| | n | Rate per 28 days | Active vs. Placebo | P-value | n | Rate per 28 days |
| Overall | [redacted] | | | | | |
| Region | | | | | | |
| North America | [redacted] | | | | | |
| Europe | [redacted] | | | | | |
| Sex | | | | | | |
| Male | [redacted] | | | | | |
| Female | [redacted] | | | | | |
| Race | | | | | | |
| White | [redacted] | | | | | |
| Other | [redacted] | | | | | |
| Baseline attack rate | | | | | | |
| ≥2 attacks/month | [redacted] | | | | | |
| <2 attacks/month | [redacted] | | | | | |
| Age (years) | | | | | | |
| 12 to 17 | [redacted] | | | | | |
| 18 to 64 | [redacted] | | | | | |
| ≥ 65 | [redacted] | | | | | |
| Weight[b] | | | | | | |
| < median | [redacted] | | | | | |
| ≥ median | [redacted] | | | | | |
| BMI[c] | | | | | | |
| Healthy weight | [redacted] | | | | | |
| Overweight | [redacted] | | | | | |
| Obese | [redacted] | | | | | |
| Prior androgen use | | | | | | |
| Yes | [redacted] | | | | | |
| No | [redacted] | | | | | |

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). [b] The median weight of the ITT population was 78.96 kg. [c] 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

Source: APeX-2 CSR[45]

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; ITT, intent to treat; N, number of patients.



## *B.2.8 Meta-analysis*

All efficacy and safety data relevant to this appraisal are provided from one relevant Phase III RCT, APeX-2, therefore, it was not necessary to conduct a meta-analysis.

## *B.2.9 Indirect and mixed treatment comparisons*

APeX-2 is a robust RCT, directly comparing berotralstat and placebo, the comparator of interest for this submission. An indirect treatment comparison is not considered necessary to provide additional evidence to support this submission.

## *B.2.10 Adverse reactions*

### B.2.10.1 Exposure

The mean durations of exposure to berotralstat 150 mg and placebo for patients in Part 1 were [redacted] days and [redacted] days, respectively. For further details, see Table 16.

**Table 16: Summary of Treatment Exposure (Safety Population)**

| Exposure Outcome | Berotralstat 150mg; N=40 | Placebo; N=39 |
|---|---|---|
| Duration of exposure (days)[a] | | |
| Mean (SD) | [redacted] | [redacted] |
| Median | [redacted] | [redacted] |
| Range | [redacted] | [redacted] |
| Duration of exposure, n (%)[a] | | |
| ≤ 84 days (≤ 12 weeks) | [redacted] | [redacted] |
| 85 to 168 days (>12 to ≤ 24 weeks) | [redacted] | [redacted] |
| 169 to 252 days (>24 to ≤ 36 weeks) | [redacted] | [redacted] |
| Person-years of exposure (years)[b] | [redacted] | [redacted] |

Notes: [a] The duration of exposure in Part 1 was calculated as last dose date - first dose date + 1. [b] Person-years of exposure was calculated for each patient as (last dose date - first dose date + 1)/365.25 and then summed across all patients in a given dose group in Part 1.

Source: APeX-2 CSR[45]
Abbreviations: N/n, number of patients; SD, standard deviation

### B.2.10.2 Incidence

No patient in the berotralstat 150 mg group experienced a treatment-emergent SAE or a drug-related Grade 3 or 4 TEAE. 85% of berotralstat patients, and 77% of placebo patients experienced a TEAE during Part 1. Forty percent of berotralstat treated patients experienced a drug-related TEAE. All study drug related TEAEs were mild to moderate. One berotralstat patient discontinued the drug due to a TEAE. A summary of the TEAEs is presented in Table 17.

**Table 17: Overall Summary of TEAEs (Safety Population)**

| TEAE Summary | Berotralstat 150 mg; N=40 n (%) | Placebo; N=39 n (%) |
|---|---|---|
| Number of patients with: | | |
| Any TEAE | 34 (85.0%) | 30 (76.9%) |
| Any drug-related TEAE[a] | 15 (37.5%) | 13 (33.3%) |
| Any SAE | 0 | 3 (7.7%) |
| Any drug-related SAE | 0 | 0 |
| Any Grade 3 or 4 TEAE | [redacted] | [redacted] |
| Any drug-related Grade 3 or 4 TEAE | 0 | 0 |
| Any TEAE leading to interruption of study drug[b] | [redacted] | [redacted] |
| Any TEAE leading to discontinuation of study drug | 1 (2.5%) | 1 (2.6%) |
| Any investigator-identified rash[c] | 1 (2.5%) | 0 |
| Any GI abdominal TEAE[d] | 20 (50.0%) | 14 (35.9%) |
| Any GI abdominal TEAE leading to discontinuation of study drug | 0 | 0 |

Notes: [a] A drug-related TEAE was defined as any AE where the investigator defines the relationship to blinded study drug as Possibly Related, Probably Related, or Definitely Related. [b] An AE leading to interruption of study drug was any AE where the Action Taken on the AE eCRF was marked as 'Drug Interrupted'. [c] An investigator-identified rash was any AE that the investigator noted as an AE of special interest on the AE eCRF. [d] GI abdominal AE was any AE with a PT within the MedDRA 19.1 hierarchy under the High-level Group Terms of 1) GI signs and symptoms or 2) GI motility and defaecation conditions.

Source: ApeX-2 CSR[45]
Abbreviations: AE, adverse event; eCRF, electronic case report form; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; n, number of patients who experienced the event; PT, preferred term; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

The most frequently reported TEAEs are summarised in Table 18 by incidence. The most frequently reported TEAEs were nasopharyngitis, nausea, and vomiting. Nasopharyngitis and nausea were more commonly reported on placebo than either berotralstat arm.

**Table 18: 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[45]
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.

### Deaths and serious adverse events

No deaths occurred during the time period covered by the study.

No treatment-emergent SAEs were considered related to study treatment. Further details are provided in

Table ***19***.

**Table 19: Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)**

| System Organ Class Preferred Term | Berotralstat 150mg; n=40 n (%) [events] | Placebo; n= 39 n (%) [events] |
|---|---|---|
| Any SAE | [redacted] | [redacted] |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | [redacted] | [redacted] |
| Plasma cell myeloma | [redacted] | [redacted] |
| Uterine leiomyoma | [redacted] | [redacted] |
| Gastrointestinal disorders | [redacted] | [redacted] |
| Diverticulum intestinal haemorrhagic | [redacted] | [redacted] |
| Infections and infestations | [redacted] | [redacted] |
| Pneumonia | [redacted] | [redacted] |
| Nervous system disorders | [redacted] | [redacted] |
| Transient ischaemic attack | [redacted] | [redacted] |

Source: ApeX-2 CSR[45]
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.

## *B.2.11 Ongoing studies*

There are no ongoing studies that will provide additional evidence in the next 12 months for the indication being appraised.

## *B.2.12 Innovation*

Berotralstat offers an innovative new therapy option for HAE patients. Berotralstat is the first orally available targeted kallikrein inhibitor for prevention of HAE attacks, with a demonstrated ability to reduce the frequency of angioedema attacks. Over the course of the 24 weeks of the phase III APeX-2 trial, 50% of patients treated with 150mg of berotralstat QD experienced at least a 70% reduction in frequency of attacks from baseline.[50] Data available from Part 2 of APeX-2 indicates that the reduction rate of HAE attacks is not just maintained but improved over time on berotralstat, with no waning effect observed.

Berotralstat is the first effective treatment for HAE to offer both an oral administration route and a negligible rate of adverse events. This is unique when comparing to the other prophylactic treatments within this space.

No randomised, double blind, placebo controlled trials have been performed to quantify the clinical efficacy of attenuated androgens in HAE patients. Androgens are unlicensed and have a well-established history of safety and tolerability concerns associated with long-term use, including hormonal imbalances, which can result in many undesired side effects. Many patients discontinue or are unsuitable for androgen treatment, and have no treatment options that reduce the frequency of attacks. The only option left for these patients is to rely on a '*watch & rescue*' strategy consisting of acute therapies, which do not reduce the frequency of attacks, the associated anxiety over their onset, or reduce resource use for the healthcare system.[6] Berotralstat provides an effective treatment option for these patients.

For those patients appropriate for prophylaxis and ineligible (i.e. those patients who experience less than 2 attacks per week), intolerant, unable or unwilling to use IV or SC therapies, there is currently no licenced long-term prophylactic therapy that has been shown to be effective and well tolerated in clinical trials. One study on satisfaction with HAE patient therapies have found that 50% of patients prefer non-invasive methods of administration, with a second study reporting 62% of respondents who used a peripheral vein to administer treatment reported difficulty finding a vein or getting the infusion to work properly.[51,52] Fear of needles, injection site reactions, hard-to-find veins, and the increased burden on the NHS for treatment administration are all problems that could be addressed following a positive recommendation for berotralstat.

### *B.2.13 Interpretation of clinical effectiveness and safety evidence*

APeX-2 is the pivotal study for the use of berotralstat to prevent HAE attacks. The phase III randomised, double-blind, placebo-controlled, parallel group study met its primary efficacy endpoint, and berotralstat demonstrated sustained efficacy over the six months of the study. The observed reduction in HAE attacks was statistically significant in comparison to placebo (44% reduction; $p < 0.001$). Exploratory analyses indicated treatment with berotralstat QD for 24 weeks was associated with

a ≥ 50% reduction in attack rate relative to baseline in [redacted]% (p=0.005) of patients and a 70% reduction in 50% of patients [redacted]

Consequently, the number of attacks requiring treatment with acute therapies will be reduced by berotralstat, leading to a decreased burden on the NHS. This reduction was demonstrated in APeX-2, with the rate of HAE attacks requiring acute treatment decreasing by [redacted] when patients were treated with berotralstat compared to placebo.

The results of this study support the use of berotralstat at a dose of 150 mg QD for prophylaxis to prevent attacks of angioedema in patients with HAE 12 years and older.

**Safety**

Administration of berotralstat 150 mg QD was well-tolerated in this study. No patient in the berotralstat group experienced a treatment-emergent SAE or a drug-related Grade 3 or 4 TEAE. [redacted] percent of berotralstat treated patients experienced a drug related TEAE all of which were mild to moderate. One berotralstat patient discontinued the drug due to a TEAE. No patients died in APeX-2.

**Strengths of the clinical evidence**

The clinical benefit of berotralstat was sustained over time. No evidence of treatment waning was observed over Part 1 and Part 2 of APeX-2.

The robustness of these results was supported by six sensitivity analyses. All sensitivity analyses produced statistically significant results: treatment with berotralstat reduced HAE attack rates by up to at least [redacted] versus placebo.

Subgroup analyses also supported the consistency of berotralstat's effectiveness in reducing the rate of HAE attacks [redacted]

The patient population of APeX-2 is representative of those in UK clinical practice. The trial included sites in the UK and enrolled patients who were representative of the patients who would receive berotralstat in routine clinical practice in the UK. The benefits reported from this trial are likely to be reflected in clinical practice in England and Wales.

**Limitations of the clinical evidence**

One limitation of the clinical evidence for berotralstat is the small sample size in APeX-2, which is a typical challenge when assessing rare diseases. However, the 121 patients included in APeX-2 represent a relatively large population when compared to the sample sizes of studies for other treatments in HAE. The pivotal studies for Cinryze, Haegarda, and lanadelumab had 22, 90, and 125 patients, respectively.

A second limitation is that there is no data available on the efficacy and safety of berotralstat beyond 96 weeks (Part 3). However, data available up to 48 weeks from Part 2 of APeX-2 showed a sustained clinical benefit for berotralstat.

Thirdly, The EQ-5D data collected in APeX-2 is suboptimal, due to its collection not aligning with the onset of HAE attacks. As such it may not be appropriate to characterise HRQoL in patients with HAE.

**End of life criteria**

Berotralstat does not meet the criteria for ‘life-extending treatment at the end of life'.

## B.3 Cost effectiveness

- A two-state Markov model was developed to evaluate the cost-effectiveness of berotralstat versus SoC in HAE patients, who experience 2 or greater attacks per month per month at baseline, and have previously received treatment with androgens.

- The model structure consists of two states: alive and dead. Within the alive health state, patients accumulate costs and QALYs depending on how much time they spend experiencing an HAE attack or attack-free.

- Clinical data used in the economic analysis was sourced from the APeX-2 RCT. The time spent experiencing HAE attacks is based on the relative reduction in attack rate and duration of attacks for berotralstat and SoC patients. Attack location data was used to inform HRQoL and resource use. A treatment continuation rule was applied such that only those patients who experience a 50% or greater reduction in attack rate versus baseline after 3 months continue to receive berotralstat.

- Utility values were sourced from previously published EQ-5D data for HAE patients during both attack and attack free episodes, as well as a TTO study designed to elicit the utility values that represent the caregiver burden. The disutility associated with an attack is separated by attack location. Background utility is adjusted by age throughout the time horizon.

- Costs associated with prophylactic treatment and acute treatment of HAE attacks are considered in the economic analysis. All costs are from relevant UK sources. Resource use associated with attacks was informed by UK clinicians and are separated by attack location. The key cost drivers in the economic model are the prophylactic acquisition costs and acute therapy costs during an attack.

- The base case results show [redacted] incremental QALYs gained as a result of the use of berotralstat for [redacted] incremental costs. This results in an ICER of

£20,707 per QALY gained. This is below the cost-effective acceptability threshold of £30,000 specified by NICE.

- Sensitivity analysis, in the form of PSA and OWSA, show that [redacted] of 1,000 simulations remained below the £30,000 cost effectiveness threshold, and that the model is most sensitive to variation in the baseline attack rate for SoC patients and the percentage of attacks treated for SoC. This demonstrates the robustness of the economic analysis despite variation to key input values.

- Scenario analysis results demonstrate the inclusion of administration-based utility benefit, adjusting the use of acute treatment to align with UK clinical practice, and taking a societal perspective all improve the cost effectiveness of berotralstat compared against SoC.

- All key model inputs and modelling assumptions have been validated by UK clinicians or independent health economics experts.

### *B.3.1 Published cost-effectiveness studies*

An economic systematic literature review (SLR) was conducted to identify cost-effectiveness, health-related quality of life (HRQoL) (Section B.3.4), and cost and resource use studies (Section B.3.5). Full details of the methodology and results of the SLR are detailed in Appendix G, Appendix H, and Appendix I.

### *B.3.2 Economic analysis*

The economic SLR did not identify any studies that assessed the cost-effectiveness of berotralstat as a treatment for patients aged 12 years or older with HAE, therefore it was necessary to develop a de-novo cost-effectiveness analysis. The details of this analysis are provided in the following sections.

#### B.3.2.1 Patient population

The cost-effectiveness analysis considers patients aged 12 years or older with Type 1 or 2 HAE who experience:

- two or more clinically significant attacks per month and are unsuitable for, or refractory to, androgens.

- two or more clinically significant attacks per week and are unsuitable for regular injectable prophylaxis with lanadelumab or C1-INHs.

This patient population was selected instead of the broader population specified in the NICE scope as it was determined, based on discussions with UK clinical experts and the UK patient group, that this was the patient group with the highest level of unmet need under current clinical practice. Patients within this population do not currently have access to prophylactic treatment options and are limited to acute treatments, which only provide mitigation of symptoms and do not provide any reduction in the frequency of attacks.

This patient population is representative of a large proportion of HAE patients in the UK. Discontinuation of attenuated androgens is common due to the safety and tolerability issues strongly associated with their use, which are exacerbated further by longevity of treatment duration.[6] Licensed prophylactic therapies such as C1-INHs and lanadelumab are not effective in all patients and under the current NHS commissioning policy are only available for the patients with the most extreme manifestations of the condition (≥2 attacks per week) despite the use of oral prophylaxis.[30] There are significant issues with IV and SC administration such as pain, invasion, risk of infection, venous access leading to problems associated with venous exhaustion, scars, and anxiety associated with needle use that may lead patients to discontinue or seek an alternative treatment to C1-INHs or lanadelumab.[53] It is estimated approximately only 8% of HAE patients in the UK receive routine C1-INH or lanadelumab injections as a long-term prophylactic therapy.[28] This highlights the substantial unmet need within the indicated population.

The APeX-2 RCT did not include the targeted patient population as a prespecified subgroup, therefore it was necessary to conduct post-hoc analyses to create a patient group who are representative of the chosen population. This was done by combining the following two pre-specified subgroups:

- Patients with 2 or more clinically significant HAE attacks per month at baseline.

- Patients who had received previous treatment with attenuated androgens at baseline.

The combination of sub-populations inform the data for the patients entering the economic analysis (N=35). The relative comparability of this sub-population and the indicated population is discussed below:

- It was assumed that patients who are unsuitable for, or refractory to, attenuated androgens show similar levels of safety and efficacy as patients who discontinued attenuated androgen use before enrolling in APeX-2. It is reasonable to assume that if a patient has discontinued androgen treatment, they were in some way unsuitable for, or refractory to, treatment. The assumption was required because data was not collected prior to enrolment in APEX-2 as to whether patients were unsuitable or refractory to attenuated androgens.

- It is assumed that patients with two or more clinically significant HAE attacks per week would show similar levels of efficacy to those patients who experienced fewer than two attacks per week at baseline. This assumption was necessary because no patients enrolled in the APeX-2 study experienced two or more attacks per week at baseline. This population accounts for approximately 8% of HAE patients in the UK.

### B.3.2.2 Model structure

A cohort-based Markov model was developed in Microsoft Excel® to assess the cost-effectiveness of berotralstat in HAE. The model includes two main health states:

- Alive: Patients in this health states are alive and can accumulate costs and QALYs.

- Dead: Patients in this stage are dead and cannot accumulate costs and QALYs.

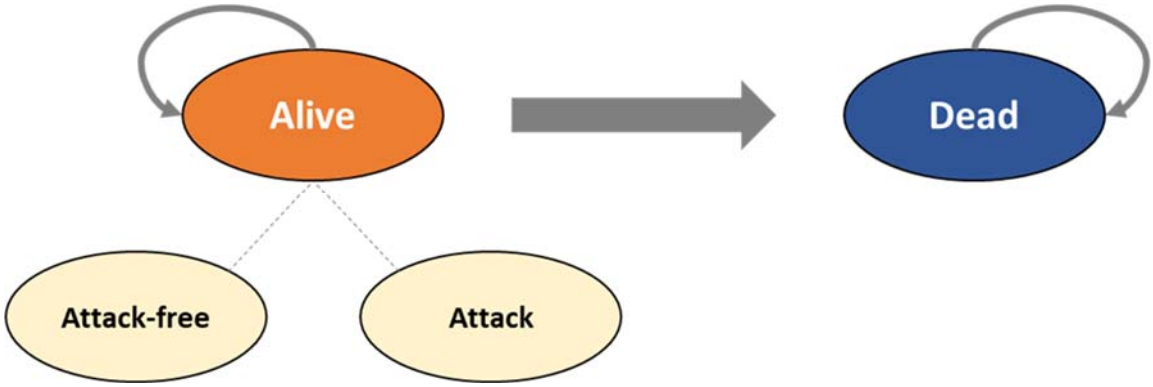
Within the ‘Alive’ health state there are two sub-states:

- Patients who are currently experiencing an HAE attack.
- Patients who are currently attack-free.

As HAE is a persistent condition characterised by acute attacks, this model structure accurately captures the nature of the condition and disease trajectory. Patients in the ‘attack’ state accumulate more costs and fewer QALYs than those in the ‘attack-free’ state since most of the negative health effects and costs associated with HAE are related to attacks. The time spent in the ‘attack-free’ and ‘attack’ states was determined by treatment-specific attack rates and the duration of attacks as observed in APeX-2.

The economic model structure is presented in Figure 11.

**Figure 11: Model structure**




### B.3.2.3 Cycle length

The cycle length used within the economic model is 28 days. All references within this submission to a ‘month’ are defined as 28 days. This cycle length was chosen as it aligns with the APeX-2 trial, in which data was collected at 28-day timepoints, and previous NICE submissions in HAE.[7]

A half-cycle correction was applied to both costs and health benefits in the Markov model in accordance with conventional modelling standards. This accounts for the

fact that attacks may occur at any point during a cycle rather than exclusively at end/beginning of each cycle.[54]

### B.3.2.4 Time horizon

HAE is a condition which affects patients for their entire life. It is appropriate to apply a lifetime time horizon so that all costs and QALYs associated with treatment could be captured. The mean age of patients entering the model is 44 years, based on the average age observed in the subgroup of patients with 2 or more attacks per month and previous androgen use at baseline in APeX-2. Patients are assumed to live a maximum of 100 years, so the lifetime time horizon is calculated as 56 years.

### B.3.2.5 Key features of the economic analysis

There is one other appraisal for this indication to date, namely TA606 'Lanadelumab for preventing recurrent attacks of hereditary angioedema'. The key features of the economic model that were accepted by the appraisal committee in TA606 are presented alongside the key features of this submission, along with justification for any deviation from the values used within TA606, are presented in Table 20.

**Table 20: Features of the economic analysis**

| | Previous appraisals | Current appraisal | |
|---|---|---|---|
| **Factor** | **TA606** | **Chosen values** | **Justification** |
| Time horizon | Lifetime (60 years) | Lifetime (56 years) | The reference case stipulates that *'the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared'.*[55]<br>A lifetime time horizon was appropriate to satisfy the prescribed criteria due to the life-long nature of HAE. The mean age of the patients entering the economic model are 44 years old. This is based on the mean age of the of patients within the sub-population of interest at baseline in the APeX-2 trial. Patients are assumed to live a maximum of 100 years, so a lifetime time horizon is calculated as 56 years. |
| Cycle length | 28 days | 28 days | This cycle length aligns with that used within the APeX-2 trial and previous NICE submissions.[56] |
| Discount for utilities and costs | 3.5% | 3.5% | Aligns with NICE reference case. |
| Perspective (NHS/PSS) | UK NHS/PSS | UK NHS/PSS | NICE reference case. |

| | | | |
|---|---|---|---|
| Source of utilities | Attack utility values were based on EQ-5D-5L data from Nordenfelt (2014)[57]<br><br>Treatment administration utilities were based on data from Jørgensen (2017)[58]<br><br>Caregiver disutilities were not considered. | 'Attack' and 'attack free' utilities were based on EQ-5D-5L data from Nordenfelt (2014)[57]<br><br>Caregiver disutilities were informed by a TTO study commissioned by BioCryst Pharmaceuticals.<br><br>Scenario analyses:<br>'Attack' and 'attack free' utilities informed by a TTO study commissioned by BioCryst<br>Treatment administration utilities based on data from Holko (2018)[59] | EQ-5D data was collected during APeX-2, however due to the irregular nature of HAE it would be unlikely that EQ-5D data collection would have coincided with the onset of an attack. The EQ-5D data collected as part of the APeX-2 study is not a reliable measure of the HRQoL for patients with HAE.<br><br>In response to this lack of validity, the 'Attack' and 'attack free' utilities are informed by the utility values presented in Nordenfelt (2014)[57].<br><br>BioCryst conducted a time trade off (TTO) study to elucidate utility decrements experienced by caregivers. The results of the TTO study have been used to inform the disutility experienced by caregivers within the economic model. |
| Source of costs | NHS reference costs, literature and expert opinion | BNF costs. NHS reference costs. PSSRU costs.<br>Expert opinion | Unit costs are obtained from UK national resources where possible to reflect UK NHS/PSS perspective. The APeX-2 trial and clinical opinion were used to inform resource use. Wider literature searches provided additional information. |

Abbreviations: BNF, British National Formulary; EQ-5D, EuroQol 5 dimensions; HAE, Hereditary angioedema; N/A, Not Applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services; PSSRU, Personal Social Services Research Unit; QALY, Quality Adjusted Life Year; TTO, Time trade off; UK, United Kingdom.

### B.3.2.6 Intervention technology and comparators

The intervention of interest in this submission is berotralstat, a small molecule inhibitor of plasma kallikrein indicated for the prevention of acute attacks in patients aged 12 years or older. Only the berotralstat 150mg QD dosing regimen is considered in this submission, as this is the only dose that is under assessment by the EMA. Berotralstat has been awarded an EAMS positive scientific opinion and holds a PIM designation from the MHRA in the UK. If approved, berotralstat would be the only oral therapy licensed for use as a treatment for the prevention of HAE attacks in the UK.

Standard of care (SoC) is the only comparator of interest in this submission. SoC is defined as: avoidance of triggers known, or suspected, to cause HAE attacks, combined with acute treatment of HAE attacks as they occur. This differs from comparators specified in the NICE scope for the following reasons:

- **Attenuated androgens** are not licensed as a long-term prophylactic treatment in HAE, though they are used off label. Long term use of attenuated androgens is often discontinued due to safety and tolerability concerns associated with their use.[6] The anticipated population for berotralstat are those patients that are unsuitable for, or refractory to, androgens. Patients entering the economic analysis will have already discontinued or been considered unsuitable and advised against androgen use as part of their treatment strategy. Therefore, androgens are not considered direct comparators to berotralstat in the UK clinical setting.

- **C1 esterase inhibitors:** The current treatment guidelines for HAE stipulate that patients are eligible for consideration for use of routine C1-INH injections if they are experiencing two or more clinically significant attacks per week, despite treatment with oral prophylactic therapy.[30] This eligibility criteria means that the majority of HAE patients are ineligible for treatment with routine C1-INH in clinical practice. There are also a number of patients who are unsuitable for regular injectable therapies due to issues such as phobia of needles, inability to locate suitable veins and venous exhaustion. The anticipated population for berotralstat considers those patients that are

ineligible, unsuitable, contraindicated or refractory to routine C1-INH. Therefore, C1-INH are not considered direct comparators to berotralstat in clinical practice.

- **Lanadelumab:** Under current NICE guidelines, patients are eligible for consideration of the use of lanadelumab if they fulfil the eligibility criteria for routine C1-INH.[60] The anticipated population for berotralstat considers those patients who are ineligible, unsuitable, contraindicated or refractory to lanadelumab. Lanadelumab is not a direct comparator to berotralstat in clinical practice for these reasons.

- **Anti-fibrinolytics:** such as tranexamic acid, are indicated as a short-term prophylaxis in HAE patients but not as a long-term prophylactic. There is very limited evidence to support the clinical effectiveness of tranexamic acid in the prevention of acute attacks in HAE patients.[61] Tranexamic acid no longer appears in the guidelines as a long-term prophylactic therapy for HAE patients.[61,62] Anti-fibrinolytics are not considered a direct comparator to berotralstat in clinical practice, due to tranexamic acid only being indicated as a short-term prophylaxis, and the lack of the evidence to support its clinical efficacy.

SoC was determined to be the only comparator in the patient population relevant to this submission.

Patients receiving both berotralstat and SoC require acute treatment to alleviate symptoms when they experience HAE attacks. In this submission, patients are assumed to receive either one, or a combination of, the following acute treatments when experiencing an attack:

- Intravenous C1-esterase inhibitor (Berinert®)
- Intravenous C1-esterase inhibitor (Cinryze®)
- Subcutaneous bradykinin receptor Icatibant (Firazyr®)
- Intravenous recombinant C1-esterase inhibitor (Ruconest®)

These treatments and their respective use were based upon observed data in APeX-2 and discussions with UK clinical experts.

Please see Section B.1.2 for further details of the current treatment landscape for HAE in the UK and the place of berotralstat within this landscape.

### B.3.2.7 Continuation rule

A continuation rule for berotralstat treatment was deemed appropriate following discussions with UK clinical experts. This would ensure that modelled treatment of berotralstat would closely resemble clinical practice, only patients who benefitted from berotralstat treatment continued to receive it, and that berotralstat would remain a cost-effective option for treating patients with HAE.

A Delphi panel of UK clinical experts reached a consensus that 3 months after treatment initiation would be a suitable timepoint to assess whether treatment with berotralstat had been successful. Clinicians agreed that a 50% or greater reduction in attack frequency compared to baseline would constitute treatment success.[9]

As detailed in B.2.6.4, [redacted]% of berotralstat patients in APeX-2 experienced a 50% or greater reduction in attack rate compared to baseline after 6 months of treatment, and, as demonstrated in B.2.6.1, the treatment effect of berotralstat occurred early in the trial and was maintained from then onwards. It is reasonable to assume that the response criteria for the continuation rule could be achieved by the specified timepoint by a substantial proportion of patients. This was confirmed in post-hoc analyses detailed in section B.3.3.2.

The following continuation rule is proposed for patients who receive berotralstat treatment in the UK:

- After 3 months of treatment with berotralstat, only those patients with a ≥50% reduction in attack frequency from baseline should continue to receive berotralstat.

For those patients who do experience a ≥50% reduction in attack frequency after 3 months, treatment with berotralstat is to be continued indefinitely, assuming no safety concerns or changes in patient preference arise.

Those patients who do not experience a ≥50% reduction in attack frequency after 3 months are assumed to revert to SoC.

There will be no additional monitoring requirements needed to implement this continuation rule. The assessment of treatment response at 3 months will be incorporated into routine health care consultations, which patients would be expected to attend regardless of treatment regimen, i.e. regular specialist consultation.

This continuation rule will ensure that only patients for whom berotralstat is a cost-effective treatment option will receive treatment, as those who do not experience sufficient health benefits will stop treatment, and in turn stop incurring costs.

### *B.3.3 Clinical parameters and variables*

The clinical data used to inform the parameters in the base case economic analyses are sourced from post-hoc analyses of the following subgroup from APeX-2:

- Patients with ≥2 attacks per month and previous use of androgens at baseline (N=35).

The rationale for the use of this subgroup is given in Section B.2.3.1.

#### B.3.3.1 Baseline demographics

The baseline demographics for patients entering the economic model are based on data observed for the sub-population of interest within the APeX-2 trial, collated for both treatment arms. The baseline demographic values are presented in Table 21.

**Table 21: Baseline demographics for patients entering the economic model**

| Baseline demographics | Combined for berotralstat and SoC |
|---|---|
| Mean age | [redacted] |
| Percentage female | [redacted] |
| Mean weight (kg) | [redacted] |

Source: APeX-2
Abbreviations: SoC, standard of care; kg, kilograms

### B.3.3.2 Treatment response

As specified in Section B.3.2.7, only patients who achieve a 50% or greater reduction in attack rate by month 3 will continue treatment with berotralstat.

A post-hoc analysis demonstrated that [redacted] of patients in the sub-population of interest met the criteria for this continuation rule.

### B.3.3.3 All cause treatment discontinuation

Consideration has been given to patients that may discontinue berotralstat over time due to other external factors. This is referred to as 'background discontinuation'.

Patients that may discontinue due to a lack of response are assumed to be accounted for by the continuation rule which assumes non-responders discontinue treatment at 3 months.

It is assumed that there is no treatment waning effect that would cause a loss of response leading to treatment discontinuation in the base case analysis.

As discussed in section B.2.10, discontinuation due to the adverse effects of berotralstat treatment was negligible in APeX-2. Only one patient receiving 150mg QD of berotralstat discontinued treatment due to any TEAE.

As a result, it was assumed that no patients discontinue berotralstat due to background discontinuation in the economic analysis.

### B.3.3.4 Attack rate

The primary efficacy measure used to establish the clinical benefit of berotralstat compared against SoC is the reduction in attack rate from baseline. The baseline attack rate per month for the patients entering the economic model are presented in Table 22.

**Table 22: Baseline attack rates for patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| | Berotralstat | SoC |
|---|---|---|
| Baseline attack rate per month | [redacted] | [redacted] |

Source: APeX-2

Abbreviations: SoC, standard of care

The reductions in attack rate from baseline are calculated using the attack rates observed for each month of the APeX-2 trial in the base case analysis. In part 1 of APeX-2 the attack rate for each patient was recorded every month for the first 6 months. The mean attack rates for patients experiencing ≥2 attacks per month and previous use of androgens at baseline for the first 6 months are presented for both berotralstat and SoC in Table 23.

**Table 23: Mean number of attacks per month from baseline to month 6 for patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| Treatment | Mean number of attacks | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline | Month 1 | Month 2 | Month 3 | Month 4 | Month 5 | Month 6 |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Source: APeX-2
Abbreviations: SoC, standard of care

Data was available from Part 2 of APeX-2 to inform monthly attacks rates for berotralstat patients from months 7 to 12. The attack rates from months 7 to 12 for berotralstat patients are presented in Table 24.

**Table 24: Mean number of attacks per month from month 7 to month 12 for patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| Treatment | Mean number of attacks | | | | | |
|---|---|---|---|---|---|---|
| | Month 7 | Month 8 | Month 9 | Month 10 | Month 11 | Month 12 |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Source: APeX-2

The attack rate for responders, as defined by the continuation rule, were applied to all patients that continued to receive berotralstat after month 3. Responders are considered to be those patients that achieved a 50% or greater reduction in attack rate from baseline by month 3. The attack rate for responder patients from months 4 to 12 are presented in Table 25.

**Table 25: Mean number of attacks per month from month 4 to month 12 for responder patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| Treatment | Mean number of attacks | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Month 4 | Month 5 | Month 6 | Month 7 | Month 8 | Month 9 | Month 10 | Month 11 | Month 12 |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Source: APeX-2

The final attack rates applied in the economic analysis, including the impact of the implementation of the continuation rule, are presented in Table 26, along with the associated percentage change from baseline for each cycle.

**Table 26: Mean number of attacks per month from month 0 to month 12 that inform the economic analysis**

| Month | Number of attacks | | Percentage change from baseline | |
|---|---|---|---|---|
| | Berotralstat | SoC | Berotralstat | SoC |
| 0 | [redacted] | [redacted] | [redacted] | [redacted] |
| 1 | [redacted] | [redacted] | [redacted] | [redacted] |
| 2 | [redacted] | [redacted] | [redacted] | [redacted] |
| 3 | [redacted] | [redacted] | [redacted] | [redacted] |
| 4 | [redacted] | [redacted] | [redacted] | [redacted] |
| 5 | [redacted] | [redacted] | [redacted] | [redacted] |
| 6 | [redacted] | [redacted] | [redacted] | [redacted] |
| 7 | [redacted] | [redacted] | [redacted] | [redacted] |
| 8 | [redacted] | [redacted] | [redacted] | [redacted] |
| 9 | [redacted] | [redacted] | [redacted] | [redacted] |
| 10 | [redacted] | [redacted] | [redacted] | [redacted] |
| 11 | [redacted] | [redacted] | [redacted] | [redacted] |
| 12 | [redacted] | [redacted] | [redacted] | [redacted] |

Source: APeX-2
Abbreviations: SoC, standard of care

The attack rates beyond the 12 months for berotralstat patients and 6 months for SoC patients of observed data for each treatment are estimated using the 'last observation carried forward' approach. This assumes that the attack rate remains constant over the remainder of the time horizon at the rate observed in the final observation. The rates that are assumed to continue for the remainder of the time horizon are [redacted] and [redacted] for berotralstat and SoC respectively.

### B.3.3.5 Attack location

Attack location is the primary differentiation measure for attacks used in the economic analysis and is used to inform the impact of different types of HAE attacks on patient QoL and resource use.

Attack duration combined with attack location operates as a proxy for attack severity. Attack severity was patient-defined in APeX-2, and was therefore a subjective outcome by its nature.. Therefore, objective outcomes were used instead.

Attacks in APeX-2 were split into three locations: 'abdominal/thoratic', 'limb or other' or 'laryngeal'. The distribution of attacks at each location observed in APeX-2 for both treatment arms is presented in Table 27.

**Table 27: Location of attacks observed in the APeX trials for patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| Attack location | Berotralstat | SoC |
|---|---|---|
| Abdominal/thoratic | [redacted] | [redacted] |
| Limb/other | [redacted] | [redacted] |
| Laryngeal | [redacted] | [redacted] |

Source: APeX-2
Abbreviations: SoC, standard of care

### B.3.3.6 Attack duration

The duration of HAE attacks observed in APeX-2 is used to inform the amount of time patients spend in the 'attack' sub-state in the economic model. This impacts how patients accumulate costs and QALYs.

The mean duration of HAE attacks observed in the sub-population of interest APeX-2 trial is presented in Table 28.

**Table 28: Mean attack duration for patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| Variable | Berotralstat | SoC |
|---|---|---|
| Mean attack duration (hours) | [redacted] | [redacted] |

Source: APeX-2
Abbreviations: SoC, standard of care

### B.3.3.7 Mortality

Laryngeal HAE attacks are associated with increased mortality in undiagnosed patients, however there is very limited evidence regarding deaths due to asphyxiation caused by laryngeal HAE attacks for patients who are receiving prophylactic treatment.[3] As such, the cost effectiveness analysis did not consider any disease specific mortality. This was a conservative assumption.

Background mortality within the economic model was informed by life tables sourced from the office of national statistics (ONS) years 2016-2018 matched for age and gender for the patients entering the economic model.[63]

### B.3.3.8 Adverse events

The safety profile of berotralstat has been evaluated in Section B.2.10, which demonstrates that no SAEs or drug-related grade 3 or 4 TEAEs were observed in patients treated with berotralstat 150mg during the APeX-2 study. All study drug related TEAEs were mild or moderate for all patients receiving 150mg QD of berotralstat.

It is standard methodology for only grade 3 or 4 AEs that occur in greater than 5% of patients in either treatment arm to be considered relevant; as mild or moderate AEs are not significant enough to contribute to cost or HRQoL within the cost-effectiveness analysis. It is assumed that the impact of adverse events on the economic analysis is negligible. As such, adverse events have been omitted from the economic model.

#### B.3.3.9 Clinical expert selection process

A number of variables used in the economic analysis were either not recorded as a part of APeX-2 or were not available from published literature. In these circumstances clinical expert opinion was sourced to provide insight as to realistic values for parameters based on what has been observed in clinical practice. Expert opinion used to inform clinical parameters in the economic analysis was primarily sourced from a Delphi panel.[9]

The Delphi panel was designed to generate a consensus amongst clinicians as to realistic parameter values observed in clinical practice. The Delphi panel was structured as two rounds of surveys. In the first round each clinician is asked to respond to a number of questions anonymously. A statistical representation of the responses from the first round, which represents the “group response”, is then provided to each clinician. Clinicians are then asked to complete the survey for a second time, now taking into consideration the “group response” from the first round. The results of the second round of surveys are assumed to represent the group consensus.[9]

The only clinical variables informed by the results from the Delphi panel are the parameters that inform the continuation rule, validation for when prophylactic treatment is used and the expected place of berotralstat in the treatment pathway. The threshold for attack reduction to qualify for response and the time point at which response is assessed were derived from this Delphi process. More details can be found in section B.3.2.3.

### *B.3.4 Measurement and valuation of health effects*

#### B.3.4.1 Health-related quality-of-life data from clinical trials

As discussed in section B.2.6.4 and Table 20, quality of life data was collected for each patient in the trial via completion of an EQ-5D-5L questionnaire at baseline and weeks 4, 8, 12, 18 and 24.

The spontaneous and unpredictable nature of HAE attacks means that it would have been rare for HAE attacks to coincide with EQ-5D data collection. It is therefore

unlikely that the EQ-5D-5L data collected in APeX-2 accurately represents the quality of life implications for either a patient experiencing an HAE attack, or a patient who is completely attack-free.

Two alternative approaches are presented to address the issue of missing utility data. The utility data for attack free and attack episodes in the base case analysis is informed using data presented in Nordenfelt et al. (2014)[57]. A scenario analysis is presented in which the utility values are source from a TTO study specifically designed to elicit utility values associated with HAE.

### B.3.4.2 Mapping

Nordenfelt et al. (2014) collected EQ-5D-5L scores which were converted to EQ-5D-3l using the UK crosswalk value set.[57,64] The TTO framework does not require mapping questionnaire responses to utility scores.

### B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify existing studies investigating the HRQoL of patients aged 12 years or older with HAE. Full details of the methodology and results can be found in Appendix H.

### B.3.4.4 Adverse reactions

As discussed in section B.3.3.6, the impact of AEs has been deemed negligible in this submission, and as such no disutility values associated with AEs are included in the base case analysis.

### B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Within the base case of the economic analysis there are three situations in which HRQoL data is applied:

- 'Baseline' attack-free utility, from which all utility decrements are deducted.
- HAE attack disutilities, where a utility decrement is applied due to experiencing an attack.

- Caregiver attack disutilities, where a utility decrement is applied to account for anxiety and loss of activities experienced by caregivers of patients with HAE.

***Nordenfelt et al. (2014)***

The utility values used in base case of the economic analysis are informed by the data presented by Nordenfelt et al. (2014),[57] which reported the results of a retrospective survey of patients from a Swedish registry. The study obtained EQ-5D-5L data for time spent attack free as well as time spent experiencing an attack.

A regression analysis was performed to quantify the impact of age and frequency of attacks on the 'attack free' and 'attack' utility weights. Age and frequency of attacks were significantly correlated with 'attack free' utility weights. Coefficients for these covariates were calculated as -0.0043 for each attack in the previous cycle and -0.02205 per ten years of age.

Equation 1 shows the formula used in Nordenfelt at al. (2014)[57] to estimate utility values for patients who were attack-free.

**Equation 1: Attack free utility formula used in the economic model**

$$\begin{aligned}&\text{attack free utility}\\&\quad = 0.825 - 0.02205 \times (10\ \text{years gained})\\&\quad - 0.0043 \times (\text{number of attacks in previous cycle})\end{aligned}$$

An average attack severity disutility was applied to all attacks irrespective of attack location. The average attack severity utility value presented in Nordenfelt et al. (2014)[57] is 0.512. The associated disutility is calculated by subtracting this value from the attack free utility value of 0.825. This results in an average attack disutility value of -0.313.

This disutility value is applied for the duration of time each patient spends in the 'attack' sub-state each cycle.

**Time trade-off study**

A scenario analysis considers utility values obtained from a TTO study commissioned by BioCryst Pharmaceuticals. The TTO study was specifically designed to obtain utility values for both patients who are experiencing HAE attacks and those who are attack-free. Details of the TTO study are presented in Appendix J. The utility values elicited from the study for use in the economic analysis are presented in Table 29.

***Caregiver disutility***

Caregiver disutility is calculated based on the age adjusted utility estimates for the UK general population and the results of the TTO study in the base case analysis. Nordenfelt et al. (2014)[57] did not report caregiver disutilities, and as such the TTO study was the only source available to inform the values for the economic model.

As described in Appendix J, the baseline utility estimate for the TTO population was calculated as [redacted]. The caregiver burden associated with HAE during attack episodes is represented by the caregiver utility value elicited from the TTO study of [redacted] The disutility that applies to caregivers associated with an attack is calculated by subtracting this value from the general population utility estimated using the TTO study demographics [redacted]

The disutility for caregivers associated with an attack is calculated to be [redacted] This utility value represents the impact on caregivers' HRQoL during an attack due to anxiety and the requirement to provide physical assistance.

The caregiver disutility is applied for all time spent experiencing an attack in the alive health state for all patients each cycle.

***Mode of administration utility benefit***

It is commonly accepted that an oral method of administration is preferred by both patients and clinicians to subcutaneous (SC) and intravenous (IV) therapies. This is due to a number of factors including: no pain due to needle use, convenience and ease of oral self-administration, reduced chance of infection, less chance of skin

irritation, avoids the issues of venous exhaustion, avoids anxiety issues associated with needles, does not require a health care professional, and many more.[58,59,65] A study by Holko et al (2018) investigated the QoL implications associated with different modes of administration of medicinal products.[59]

Disutilities associated with the mode of administration do not feature in the base case analysis, however a scenario analysis is presented in which utility values are applied for all attacks treated with either SC or IV therapies each cycle. As such, a conservative approach is used in the base case that may underestimate the utility benefits conferred by berotralstat's oral method of administration.

### B.3.4.6 Summary of utility values used within the economic analysis

The utility values used in the economic model, along with confidence intervals (where available) and justification for their inclusion, are presented in Table 29.

**Table 29: Summary of utility values for cost-effectiveness analysis**

| State | Utility value: mean (standard error) | 95% confidence interval | Reference in submission (section and page number) | Justification |
|---|---|---|---|---|
| Nordenfelt attack free utility | 0.825 | (0.618, 1) | B.3.4.5 p89 | Aligns with TA606 |
| Nordenfelt attack free utility | 0.512 | (0.213, 0.811) | B.3.4.5 p89 | Aligns with TA606 |
| Caregiver utility during an attack | [redacted] | [redacted] | B.3.4.5 p90 | Demonstrates the impact on caregivers of HAE patients during an attack. |
| TTO attack free health state | [redacted] | [redacted] | B.3.6 p104 | The TTO study was designed to elicit valid utility values for the 'attack free' sub-state |
| TTO attack free disutility | [redacted] | [redacted] | B.3.6 p104-105 | This quantifies the QoL implications of living with HAE when attack free. |
| TTO Abdominal/thoratic attack disutility | [redacted] | [redacted] | | The TTO study was designed to elicit valid utility values for the attacks separated by location |
| TTO Limb/other attack disutility | [redacted] | [redacted] | | |
| TTO Laryngeal attack disutility | [redacted] | [redacted] | | |
| Utility increment due to oral administration vs SC | 0.147 | (0.087,0.208) | B.3.6 p105 | Provides a means to quantify the benefit in QoL due to method of administration. |
| Utility increment due to oral administration vs IV | 0.164 | (0.096, 0.233) | B.3.6 p105 | |

Abbreviations: HAE, hereditary angioedema; IV, intravenous; NA, not available; QoL, quality of life; SC, subcutaneous; TTO, time trade off;

## *B.3.5 Cost and healthcare resource use identification, measurement and valuation*

An economic SLR was conducted to identify published studies that reported the cost and resource use associated the management of HAE. Full details of the methodology and results of the SLR are presented in Appendix I.

### B.3.5.1 Intervention and comparators' costs and resource use

The cost associated with the acquisition and administration of berotralstat and SoC are described in the following subsections

#### *Prophylactic treatment acquisition costs*

The treatment regimen for berotralstat is prescribed as a single 150mg capsule QD to be administered orally. A pack of berotralstat contains 28 capsules. The cost of a pack of berotralstat at the PAS price is presented in Table 30. Table 30 presents the corresponding cost of treatment for berotralstat per day, per 28-day cycle, and per annum. The cost for the acquisition of berotralstat per cycle is applied to all patients actively receiving berotralstat within the economic analysis.

A patient access scheme (PAS) has been agreed prior to submission. The PAS is applied in the form of a fixed discount per pack which equates to [redacted]% off the list price.

There are no prophylactic treatment costs associated with SoC

**Table 30: Berotralstat acquisition costs taking into consideration the PAS**

| Variable | Value |
|---|---|
| List price per pack | [redacted] |
| Cost per day | [redacted] |
| Cost per 28-day cycle | [redacted] |
| Annual cost | [redacted] |

Source: BioCryst

### *Prophylactic treatment administration costs*

It is assumed that there are no additional administrative costs associated with the use of oral therapies such as berotralstat.

### *Use of acute treatment*

Both patients receiving berotralstat and SoC receive acute treatment at the onset of HAE attacks to relieve symptoms and reduce the duration of attacks. There are four acute therapies licensed for the mitigation of symptoms of HAE attacks in the UK:

- Berinert
- Cinryze
- Firazyr
- Ruconest

While most HAE attacks require acute treatment, some do not, and equally some attacks require multiple administrations of acute treatment before symptoms completely subside. Previous appraisals in HAE have not considered the costs associated with multiple administrations of acute treatment and as such have underestimated the costs associated with HAE attacks.

The frequency of administration of acute therapies for both berotralstat and SoC patients within the economic analysis are informed by the frequencies observed in the sub-population of interest in APeX-2. The frequencies used in the economic model are presented in Table 31.

**Table 31: Administration of acute therapies observed in APeX-2 for patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| Variable | Berotralstat | SoC |
|---|---|---|
| *Attacks treated* | | |
| Proportion of attacks treated with any acute therapy | [redacted] | [redacted] |
| *Attacks treated with a single dose of acute treatment* | | |
| Proportion treated with: | [redacted] | [redacted] |

| | | |
|---|---|---|
| • Berinert: 1 dose | | |
| Proportion treated with:<br>• Cinryze: 1 dose | [redacted] | [redacted] |
| Proportion treated with:<br>• Firazyr: 1 dose | [redacted] | [redacted] |
| Proportion treated with:<br>• Ruconest: 1 dose | [redacted] | [redacted] |
| *Attacks treated with multiple doses of acute treatment* | | |
| Proportion treated with:<br>• Berinert: 1 dose<br>• Cinryze: 1 dose | [redacted] | [redacted] |
| Proportion treated with:<br>• Berinert: 1 dose<br>• Firazyr: 1 dose | [redacted] | [redacted] |
| Proportion treated with:<br>• Cinryze: 1 dose<br>• Firazyr: 1 dose | [redacted] | [redacted] |
| Proportion treated with:<br>• Firazyr: 1 dose<br>• Ruconest: 1 dose | [redacted] | [redacted] |
| Proportion treated with:<br>• Cinryze: 2 doses | [redacted] | [redacted] |
| Proportion treated with:<br>• Firazyr: 2 doses | [redacted] | [redacted] |
| Proportion treated with:<br>• Firazyr: 2 doses<br>• Berinert: 1 dose | [redacted] | [redacted] |
| Proportion treated with:<br>• Firazyr: 2 doses<br>• Cinryze: 1 dose | [redacted] | [redacted] |
| Proportion treated with:<br>• Firazyr: 2 doses<br>• Ruconest: 1 dose | [redacted] | [redacted] |
| Proportion treated with:<br>• Ruconest: 2 doses<br>• Cinryze: 1 dose | [redacted] | [redacted] |
| Proportion treated with:<br>• Cinryze: 3 doses | [redacted] | [redacted] |
| Proportion treated with:<br>• Firazyr: 3 doses | [redacted] | [redacted] |
| Proportion treated with:<br>• Firazyr: 3 doses<br>• Berinert: 1 dose | [redacted] | [redacted] |
| Proportion treated with:<br>• Cinryze: 4 doses | [redacted] | [redacted] |
| Proportion treated with:<br>• Firazyr: 4 doses | [redacted] | [redacted] |



| | | |
|---|---|---|
| Proportion treated with:<br>• Firazyr: 4 doses<br>• Berinert: 1 dose | [redacted] | [redacted] |
| Proportion treated with:<br>• Firazyr: 5 doses | [redacted] | [redacted] |
| Proportion treated with:<br>• Firazyr: 5 doses<br>• Berinert: 1 dose | [redacted] | [redacted] |
| Proportion treated with:<br>• Firazyr: 5 doses<br>• Berinert: 2 doses | [redacted] | [redacted] |
| Proportion treated with:<br>• Firazyr: 6 doses | [redacted] | [redacted] |
| Proportion treated with:<br>• Firazyr: 7 doses | [redacted] | [redacted] |
| Proportion treated with:<br>Firazyr: 10 doses | [redacted] | [redacted] |

Source: APeX-2

### *Acute therapy use informed by UK clinical experts*

A scenario analysis is presented in Appendix L, in which the use of acute therapies is informed by UK clinical experts. The responses given by experts indicate a higher use of treatments commonly associated with multiple administrations, leading to higher attack costs. As such, a conservative approach to estimating the a costs associated with treating HAE attacks is used in the base case analysis.

### *Acquisition cost of Berinert*

Dosing for Berinert is decided based on the weight of the patient at a rate of 20 IU/kg.[66] Berinert is available in either 500 or 1500unit vials costing £550 and £1,650, respectively.[67]

The mean dose of Berinert received per administration is calculated using the average weight of patients entering the economic model. The mean weight observed for patients participating in the APeX-2 trial collated across treatment arms was 86.41kg. This results in a mean dosage of 1728.21 units per administration.

The cost per administration of Berinert is £1,901 when ignoring the impact of wastage. Alternatively, considering the impact of wastage would result in the cost of Berinert as £2,200 per administration (this is not explored in this submission).

A summary of the cost considerations for Berinert in the economic analysis is presented in Table 32.

### *Acquisition cost of Cinryze*

Cinryze has a set dose of 1000 IU per administration.[66] Cinryze is available in 500 unit vials costing £1,336 for two vials.[67] This results in a cost per administration of Cinryze as £1,336. The effect of wastage is not applicable for Cinryze as the units in each pack correspond exactly to the required dose.

A summary of the cost considerations for Cinryze in the economic analysis are presented in Table 32.

### *Acquisition cost of Firazyr*

Firazyr is available in 30mg/3ml pre-filled disposable injections (POM) costing £1,395 per POM.[68] The required dose for Firazyr per administration is 30mg resulting in a cost per administration of £1,395.[69] There is no impact when considering the wastage due to the POMs being designed to deliver the recommended dose.

A summary of the cost considerations associated with the use of Firazyr are presented in Table 32.

### *Acquisition cost of Ruconest*

The recommended dose for Ruconest is 4200 units per administration for patients weighing 84kgs or over.[70] The mean weight of the patients entering the economic analysis is 86.41kg. For this reason, it is assumed that the dose of Ruconest per administration used within the economic analysis is 4200 units. Ruconest is available in the form of 2100 unit vials which cost £750 per vial.[71] The resulting cost per administration of Ruconest is £1,500.

### *Acute treatment administration costs*

Berinert, Cinryze, and Firazyr are licensed for self-administration at home, and as a result there are no additional administrative costs applied in the economic model associated with the use of these treatments.

Ruconest is not licensed for self-administration. However, UK clinicians confirmed that Ruconest is also administered at home, and therefore it is assumed that Ruconest does not accrue any additional administrative costs.

No additional administrative costs are applied in the economic analysis for use of acute therapies.

In clinical practice it is not always the case that acute therapies are administered at home, and on occasion would be performed by a medical professional accruing additional administration cost. Assuming that all administrations occur at home is a conservative approach that reduces the average cost per attack used in the economic analysis, which favours SoC.

### *Summary of acute treatment costs*

**Table 32: Summary of cost considerations for acute therapies (ignoring wastage)**

| Variable | Value | Reference |
|---|---|---|
| ***Berinert*** | | |
| Mean weight of the cohort (kg) | 86.41 | APeX-2 |
| Dose per administration | 20 units/kg = 1728.21 units | BNF[66] |
| Dosage per pack | 1500 or 500 units | BNF[67] |
| Number of packs required per administration | 2 | Calculated |
| Cost per pack (1500units) | £1,650 | BNF[67] |
| Cost per pack (500units) | £550 | BNF[67] |
| **Cost per administration (ignoring wastage)** | **£1,901** | Calculated |
| ***Cinryze*** | | |
| Dose per administration | 1000 units | BNF[66] |
| Dosage per pack | 2 X 500 units | BNF[67] |
| Number of packs required per administration | 1 | Calculated |
| Cost per pack | £1,336 | BNF[67] |
| **Cost per administration** | **£1,336** | Calculated |
| ***Firazyr*** | | |

| | | |
|---|---|---|
| Dose per administration | 30mg | BNF[69] |
| Dosage per pack | 30mg | BNF[68] |
| Number of packs required per administration | 1 | Calculated |
| Cost per pack | £1,395 | BNF[68] |
| **Cost per administration** | **£1,395** | Calculated |
| ***Ruconest*** | | |
| Dose per administration | 4200 units | BNF[70] |
| Dosage per pack | 2100 | BNF[71] |
| Number of packs required per administration | 2 | Calculated |
| Cost per pack | £750 | BNF[71] |
| **Cost per administration** | **£1,500** | Calculated |

Abbreviations: BNF, British National Formulary; kg, kilogram

The use of acute treatment is informed by the frequencies observed in APeX-2, which is presented in Table 31. This is combined with the cost per administration of acute treatment in Table 32 to calculate the average cost of treating an HAE attack for berotralstat and SoC patients, presented in Table 33.

**Table 33: Average acute therapy cost per attack**

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

Abbreviations: BNF, British National Formulary; SoC, standard of care

The average acute therapy cost per attack is lower for berotralstat, primarily due to the reduced need for multiple administrations of acute therapies for berotralstat patients compared with SoC patients.

Acute therapy costs per attack for all attacks that require acute treatment are presented in Table 33. The proportion of attacks that required treatment observed in the APeX-2 trial was [redacted] for berotralstat and [redacted] for SoC (Table 31). The average acute therapy costs are applied to [redacted] and [redacted] of attacks that occur each cycle for berotralstat and SoC, respectively.

### B.3.5.2 Health-state unit costs and resource use

Alongside the costs of acquisition of therapies there are medical resource use requirements associated with HAE attacks. Based on discussions with UK clinical experts, the following resources were identified that patients use during HAE attacks:

- A&E visits
- Hospitalisation
- Intubation
- Radiography
- Ambulance transport
- Blood tests

Resource use varies substantially across HAE attacks, and as such it was necessary to add a level of granularity rather than applying average resource use estimates to all HAE attacks. Therefore, resource use is split by attack location. Location was used instead of severity, which was patient-defined in APeX-2 and hence more subjective.

The use of these resource by HAE patients was determined through discussions with UK clinical experts during an advisory board meeting on 2nd November 2020. The experts were asked to fill in the tables below with average resource use based on their clinical experience prior to the meeting. The median values of these responses were then showed to the experts at the meeting, where any disagreements were discussed, and a consensus was reached regarding the use of resources by HAE patients in UK clinical practice.

The estimated health care resource use requirements associated with acute attacks reported by the clinical experts are presented in Table 34, considered separately for each attack location.

**Table 34: Acute attack resource use requirements**

| 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] |

Source: KOL opinion
Abbreviations: GP,General practitioner; KOL, Key Opinion Leaders

Costs are associated with each of the health care resources presented in Table 34. Where possible, the unit costs for health care resources were sourced from national databases (PSSRU[72], NHS reference costs[73]). Where unit costs were not available, assumptions were made estimating the associated cost based on the costs that were available. The cost associated with each of the health care resources used in the model, along with the source for each, are presented in Table 35.

**Table 35: Health care resource costs**

| Health care resource | Cost | Reference |
|---|---|---|
| A&E visit costs | £168.00 | NHS reference costs 18/19[73] – Service code 180 |
| Inpatient stays cost per day | £454.00 | NHS reference costs 18/19[73] – WJ11Z (non-elective short stay) |
| Intubation cost | £317.00 | NHS reference costs 18/19[73] – RN18A |
| Radiography cost | £52.00 | NHS reference costs 18/19[73] – RD40Z |
| Ambulance transport cost | £258.00 | PSSRU (2019)[72] |
| Blood test cost | £3.00 | NHS reference costs 18/19[73] – DAPS08 |

Abbreviations: GP – General practitioner; PSSRU, Personal Social Services Research; NHS, National Health Service

The average resource use requirements associated with acute attacks have been calculated by multiplying the rates of resource use presented in Table 34 with the associated costs presented in Table 35, weighted for the proportions of attacks observed at each location for each treatment arms. The calculated average resource costs associated with acute attacks are presented in Table 36 for both treatment arms.

**Table 36: Average resource costs associated with acute attacks**

| Variable | Berotralstat | SoC |
|---|---|---|
| Average resource costs associated with acute attacks | [redacted] | [redacted] |

Source: Calculated
Abbreviation: SoC, standard of care

The average resource costs associated with acute attacks are applied in the economic model for all attacks that occurs within each treatment arm each cycle.

### B.3.5.3 Adverse reaction unit costs and resource use

As discussed in section B.3.3.8 adverse events are not considered as part of the economic analysis, as such no costs or resource use associated with adverse events are reported.

### B.3.5.4 Miscellaneous unit costs and resource use

The physical dysfunction caused by HAE attacks can result in the inability to perform daily activities, including professional or academic responsibilities. A scenario analysis considering the economic implications from a wider societal perspective is presented in Appendix L. The base case analysis does not consider the economic impact associated with HAE on wider society due to loss of productivity, presenteeism, absenteeism, and reduced career prospects, and as such could be considered conservative.

## *B.3.6 Summary of base-case analysis inputs and assumptions*

**Summary of base-case analysis inputs**

A summary of variables applied in the economic analysis is presented in Table 37.

**Table 37: Summary of variables applied in the economic model**

| Variable | Value (reference to appropriate table or figure in submission) | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| Age | [redacted] | Gamma | B.3.3.1 p81 |
| Percentage female | [redacted] | Beta | B.3.3.1 p81 |
| Weight | [redacted] | Gamma | B.3.3.1 p81 |
| Discount rate costs | 3.5% | NA (fixed values) | NA |
| Discount rate outcomes | 3.5% | NA (fixed values) | NA |
| Berotralstat: baseline attack rate | [redacted] | Gamma | B.3.3.4 p82 |
| SoC: baseline attack rate | [redacted] | Gamma | B.3.3.4 p82 |
| Percentage of responders | [redacted] | Beta | B.3.3.2 p82 |
| Berotralstat: proportion of laryngeal attacks | [redacted] | Beta | B.3.3.5 p85 |
| Berotralstat: proportion of abdominal/thoratic attacks | [redacted] | Beta | B.3.3.5 p85 |
| Berotralstat: proportion of limb/other attacks | [redacted] | Beta | B.3.3.5 p85 |
| SoC: proportion of laryngeal attacks | [redacted] | Beta | B.3.3.5 p85 |
| SoC: proportion of abdominal/thoratic attacks | [redacted] | Beta | B.3.3.5 p85 |
| SoC: proportion of limb/other attacks | [redacted] | Beta | B.3.3.5 p85 |
| Berotralstat: mean attack duration (hours) | [redacted] | Gamma | B.3.3.6 p86 |
| SoC: mean attack duration (hours) | [redacted] | Gamma | B.3.3.6 p86 |
| Berotralstat: reduction in attack rate from baseline, month 1 | [redacted] | Beta | B.3.3.4 p84 |
| Berotralstat: reduction in attack rate from baseline, month 2 | [redacted] | Beta | B.3.3.4 p84 |
| Berotralstat: reduction in attack rate from baseline, month 3 | [redacted] | Beta | B.3.3.4 p84 |
| Berotralstat: reduction in attack rate from baseline, month 4 | [redacted] | Beta | B.3.3.4 p84 |
| Berotralstat: reduction in attack rate from baseline, month 5 | [redacted] | Beta | B.3.3.4 p84 |
| Berotralstat: reduction in attack rate from baseline, month 6 | [redacted] | Beta | B.3.3.4 p84 |



| | | | |
|---|---|---|---|
| Berotralstat: reduction in attack rate from baseline, month 7 | [redacted] | Beta | B.3.3.4 p84 |
| Berotralstat: reduction in attack rate from baseline, month 8 | [redacted] | Beta | B.3.3.4 p84 |
| Berotralstat: reduction in attack rate from baseline, month 9 | [redacted] | Beta | B.3.3.4 p84 |
| Berotralstat: reduction in attack rate from baseline, month 10 | [redacted] | Beta | B.3.3.4 p84 |
| Berotralstat: reduction in attack rate from baseline, month 11 | [redacted] | Beta | B.3.3.4 p84 |
| Berotralstat: reduction in attack rate from baseline, from month 12 | [redacted] | Beta | B.3.3.4 p84 |
| SoC: reduction in attack rate from baseline, month 1 | [redacted] | Beta | B.3.3.4 p84 |
| SoC: reduction in attack rate from baseline, month 2 | [redacted] | Beta | B.3.3.4 p84 |
| SoC: reduction in attack rate from baseline, month 3 | [redacted] | Beta | B.3.3.4 p84 |
| SoC: reduction in attack rate from baseline, month 4 | [redacted] | Beta | B.3.3.4 p84 |
| SoC: reduction in attack rate from baseline, month 5 | [redacted] | Beta | B.3.3.4 p84 |
| SoC: reduction in attack rate from baseline, month 6 | [redacted] | Beta | B.3.3.4 p84 |
| SoC: reduction in attack rate from baseline, month 7 | [redacted] | Beta | B.3.3.4 p84 |
| SoC: reduction in attack rate from baseline, month 8 | [redacted] | Beta | B.3.3.4 p84 |
| SoC: reduction in attack rate from baseline, month 9 | [redacted] | Beta | B.3.3.4 p84 |
| SoC: reduction in attack rate from baseline, month 10 | [redacted] | Beta | B.3.3.4 p84 |
| SoC: reduction in attack rate from baseline, month 11 | [redacted] | Beta | B.3.3.4 p84 |
| SoC: reduction in attack rate from baseline, from month 12 | [redacted] | Beta | B.3.3.4 p84 |
| Berotralstat: Attack-free utility | [redacted] | Beta | B.3.4.6 p92 |
| SoC: Attack-free utility | [redacted] | Beta | B.3.4.6 p92 |
| Berotralstat: Attack-free disutility | [redacted] | Beta | B.3.4.6 p92 |

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|---|---|---|---|
| SoC: Attack-free disutility | [redacted] | Beta | B.3.4.6 p92 |
| Laryngeal attack utility | [redacted] | Beta | NA |
| Abdominal/thoratic attack utility | [redacted] | Beta | NA |
| Limb/other attack utility | [redacted] | Beta | NA |
| Nordenfelt attack-free utility | 0.825 | Beta | B 3.4.5 p89 |
| Nordenfelt average severity attack disutility | -0.313 | Beta | B 3.4.5 p89 |
| Oral vs IV utility increment | 0.164 | Beta | B.3.4.6 p92 |
| Oral vs SC utility increment | 0.147 | Beta | B.3.4.6 p92 |
| Caregiver disutility during attack episodes | [redacted] | Beta | B.3.4.5 p90 |
| Berotralstat acquisition cost per cycle | [redacted] | Gamma | NA |
| Berotralstat compliance | [redacted] | Beta | NA |
| Berotralstat: Berinert cost per use | £1,901.03 | Gamma | B.3.5.1 p98 |
| Berotralstat: Cinryze cost per use | £1,336.00 | Gamma | B.3.5.1 p98 |
| Berotralstat: Firazyr cost per use | £1,395.00 | Gamma | B.3.5.1 p99 |
| Berotralstat: Ruconest cost per use | £1,500.00 | Gamma | B.3.5.1 p99 |
| SoC: Berinert cost per use | £1,901.03 | Gamma | B.3.5.1 p98 |
| SoC: Cinryze cost per use | £1,336.00 | Gamma | B.3.5.1 p98 |
| SoC: Firazyr cost per use | £1,395.00 | Gamma | B.3.5.1 p99 |
| SoC: Ruconest cost per use | £1,500.00 | Gamma | B.3.5.1 p99 |
| Berotralstat: Proportion of attacks treated | [redacted] | Beta | B.3.3.4 p92 |
| SoC: Proportion of attacks treated | [redacted] | Beta | B.3.3.4 p92 |
| Berotralstat: Any use of Berinert | [redacted] | Beta | NA |
| Berotralstat: Any use of Cinryze | [redacted] | Beta | NA |
| Berotralstat: Any use of Firazyr | [redacted] | Beta | NA |
| Berotralstat: Any use of Ruconest | [redacted] | Beta | NA |
| SoC: Any use of Berinert | [redacted] | Beta | NA |
| SoC: Any use of Cinryze | [redacted] | Beta | NA |



 

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|---|---|---|---|
| SoC: Any use of Firazyr | [redacted] | Beta | NA |
| SoC: Any use of Ruconest | [redacted] | Beta | NA |
| Berotralstat: Proportion treated with:<br>Berinert: 1 dose | [redacted] | Beta | B.3.5.1 p94 |
| Berotralstat: Proportion treated with:<br>Cinryze: 1 dose | [redacted] | Beta | B.3.5.1 p94 |
| Berotralstat: Proportion treated with:<br>Firazyr: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Ruconest: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Berinert: 1 dose<br>Cinryze: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Berinert: 1 dose<br>Firazyr: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Cinryze: 1 dose<br>Firazyr: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Firazyr: 1 dose<br>Ruconest: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Cinryze: 2 doses | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Firazyr: 2 doses | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Firazyr: 2 doses<br>Berinert: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Firazyr: 2 doses | [redacted] | Beta | B.3.5.1 p95 |



 

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|---|---|---|---|
| Cinryze: 1 dose | | | |
| Berotralstat: Proportion treated with:<br>Firazyr: 2 doses<br>Ruconest: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Ruconest: 2 doses<br>Cinryze: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Cinryze: 3 doses | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Firazyr: 3 doses | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Firazyr: 3 doses<br>Berinert: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Cinryze: 4 doses | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Firazyr: 4 doses | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Firazyr: 4 doses<br>Berinert: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Firazyr: 5 doses | [redacted] | Beta | B.3.5.1 p96 |
| Berotralstat: Proportion treated with:<br>Firazyr: 5 doses<br>Berinert: 1 dose | [redacted] | Beta | B.3.5.1 p96 |
| Berotralstat: Proportion treated with:<br>Firazyr: 5 doses<br>Berinert: 2 doses | [redacted] | Beta | B.3.5.1 p96 |
| Berotralstat: Proportion treated with:<br>Firazyr: 6 doses | [redacted] | Beta | B.3.5.1 p96 |



 

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|---|---|---|---|
| Berotralstat: Proportion treated with:<br>Firazyr: 7 doses | [redacted] | Beta | B.3.5.1 p96 |
| Berotralstat: Proportion treated with:<br>Firazyr: 10 doses | [redacted] | Beta | B.3.5.1 p96 |
| SoC: Proportion treated with:<br>Berinert: 1 dose | [redacted] | Beta | B.3.5.1 p94 |
| SoC: Proportion treated with:<br>Cinryze: 1 dose | [redacted] | Beta | B.3.5.1 p94 |
| SoC: Proportion treated with:<br>Firazyr: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Ruconest: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Berinert: 1 dose<br>Cinryze: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Berinert: 1 dose<br>Firazyr: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Cinryze: 1 dose<br>Firazyr: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Firazyr: 1 dose<br>Ruconest: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Cinryze: 2 doses | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Firazyr: 2 doses | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Firazyr: 2 doses<br>Berinert: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Firazyr: 2 doses<br>Cinryze: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Firazyr: 2 doses<br>Ruconest: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Ruconest: 2 doses<br>Cinryze: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Cinryze: 3 doses | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Firazyr: 3 doses | [redacted] | Beta | B.3.5.1 p95 |



 

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|---|---|---|---|
| SoC: Proportion treated with:<br>Firazyr: 3 doses<br>Berinert: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Cinryze: 4 doses | [redacted] | Beta | B.3.5.1 p95 |
| Berotralstat: Proportion treated with:<br>Firazyr: 4 doses | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Firazyr: 4 doses<br>Berinert: 1 dose | [redacted] | Beta | B.3.5.1 p95 |
| SoC: Proportion treated with:<br>Firazyr: 5 doses | [redacted] | Beta | B.3.5.1 p96 |
| SoC: Proportion treated with:<br>Firazyr: 5 doses<br>Berinert: 1 dose | [redacted] | Beta | B.3.5.1 p96 |
| SoC: Proportion treated with:<br>Firazyr: 5 doses<br>Berinert: 2 doses | [redacted] | Beta | B.3.5.1 p96 |
| SoC: Proportion treated with:<br>Firazyr: 6 doses | [redacted] | Beta | B.3.5.1 p96 |
| SoC: Proportion treated with:<br>Firazyr: 7 doses | [redacted] | Beta | B.3.5.1 p96 |
| SoC: Proportion treated with:<br>Firazyr: 10 doses | [redacted] | Beta | B.3.5.1 p96 |
| Laryngeal: Proportion of patients requiring a visit to A&E | [redacted] | Beta | B.3.5.2 p101 |
| Laryngeal: Proportion of patients requiring hospitalisation | [redacted] | Beta | B.3.5.2 p101 |
| Laryngeal: Number of days for inpatient stays | [redacted] | Gamma | B.3.5.2 p101 |
| Laryngeal: Proportion requiring intubation | [redacted] | Beta | B.3.5.2 p101 |
| Laryngeal: Proportion who receive radiography | [redacted] | Beta | B.3.5.2 p101 |
| Laryngeal: Proportion requiring ambulance transport | [redacted] | Beta | B.3.5.2 p101 |
| Laryngeal: Proportion requiring blood test | [redacted] | Beta | B.3.5.2 p101 |
| Laryngeal: Number of blood tests | [redacted] | Gamma | B.3.5.2 p101 |
| Abdominal/Thoratic: Proportion of patients requiring a visit to A&E | [redacted] | Beta | B.3.5.2 p101 |



 

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|---|---|---|---|
| Abdominal/Thoratic: Proportion of patients requiring hospitalisation | [redacted] | Beta | B.3.5.2 p101 |
| Abdominal/Thoratic: Number of days for inpatient stays | [redacted] | Gamma | B.3.5.2 p101 |
| Abdominal/Thoratic: Proportion requiring intubation | [redacted] | Beta | B.3.5.2 p101 |
| Abdominal/Thoratic: Proportion requiring radiography | [redacted] | Beta | B.3.5.2 p101 |
| Abdominal/Thoratic: Proportion requiring ambulance transport | [redacted] | Beta | B.3.5.2 p101 |
| Abdominal/Thoratic: Proportion requiring blood tests | [redacted] | Beta | B.3.5.2 p101 |
| Abdominal/Thoratic: Number of blood tests | [redacted] | Gamma | B.3.5.2 p101 |
| Limb/other: Proportion of patients requiring a visit to A&E | [redacted] | Beta | B.3.5.2 p101 |
| Limb/other: Proportion of patients requiring hospitalisation | [redacted] | Beta | B.3.5.2 p101 |
| Limb/other: Number of days for inpatient stays | [redacted] | Gamma | B.3.5.2 p101 |
| Limb/other: Proportion requiring intubation | [redacted] | Beta | B.3.5.2 p101 |
| Limb/other: Proportion requiring radiography | [redacted] | Beta | B.3.5.2 p101 |
| Limb/other: Proportion requiring ambulance transport | [redacted] | Beta | B.3.5.2 p101 |
| Limb/other: Proportion requiring blood tests | [redacted] | Beta | B.3.5.2 p101 |
| Limb/other: Number of blood tests | [redacted] | Gamma | B.3.5.2 p101 |
| A&E visit costs | £168.00 | Gamma | B.3.5.2 p101 |
| Inpatient stays cost per day | £454.00 | Gamma | B.3.5.2 p101 |
| Intubation cost | £317.00 | Gamma | B.3.5.2 p101 |
| Radiography cost | £52.00 | Gamma | B.3.5.2 p101 |
| Ambulance transport cost | £258.00 | Gamma | B.3.5.2 p101 |
| Blood test cost | £3.00 | Gamma | B.3.5.2 p101 |
| Average full-time salary in United Kingdom per year (£) | £30,414.40 | Gamma | B.3.5.2 p101 |
| Average cost lost per hour of attack | £17.63 | Gamma | B.3.5.2 p101 |

Abbreviations: A&E, accident and emergency; CI – confidence interval; NA, Not available; SoC, standard of care



 

## Assumptions

A summary of the model assumptions is provided in Table 38.

**Table 38: Assumptions underpinning the cost effectiveness analysis**

| Variable | Assumed value | Justification |
|---|---|---|
| Time horizon | 56 years | Patients entering the economic model have a mean age of 44 years. Patients are not expected to live beyond 100 years. (100 - 44 = 56). |
| Markov assumption | NA | Patients can fluctuate between the 'attack' and 'attack free' sub-states in each cycle before eventually transitioning to death. This simple structure accurately captures the course of HAE, and has been validated by expert health economists. |
| Half cycle correction | NA | A half cycle correction was applied to account for attacks that can occur mid cycle, which aligns with conventional modeling standards. |
| The population entering the economic model | Patients experiencing two or more attacks per month and prior androgen use at baseline | This is reflective of the population for this submission: patients unsuitable, or refractory to androgens or patients ineligible or unsuitable for C1-INH or lanadelumab. |
| Cycle length | 28 days | This aligns with the collection of data in APeX-2 and previous appraisals in HAE.[56] |
| Background discontinuation | Not included | The continuation rule accounts for the patients that would discontinue berotralstat due to a lack of sustained efficacy. AE rates in the trial were very low and only one patient discontinued treatment within the trial. It is reasonable to assume that responding |


 

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| | | patients will remain on berotralstat indefinitely. |
| The application of a continuation rule | Only patients who achieve a 50% or greater reduction in attack rate from baseline by month 3 will continue treatment | In clinical practice it is likely that patients who do not experience a sufficient response after initiation of berotralstat will discontinue treatment within the first few months. The definition of the continuation rule were recommended by UK clinical experts via a Delphi panel.[9] |
| Method of extrapolation for attack rates | Last observation carried forward | Alternative methods for extrapolation were explored, however due to the nature of the data it was not possible to establish a statistically valid approach that truly represents the variation in the data. The last observation carried forward assumes no additional benefit from the last observation seen, which may be considered conservative in light of the fact that treatment benefit appears to improve over time with berotralstat. |
| The use of attack location as the attack differentiation measure | NA | Severity data from the trial was patient defined with no set criteria defining the severity grades. This allows the opportunity for individual level bias. Attack location is a more objective measure that can be used to differentiate between the QoL implications and resource use associated with different attacks. |
| Disease specific mortality | Not included | Published literature and UK clinicians both suggest that disease specific mortality in diagnosed HAE patients is very minimal, with some clinicians never observing a HAE-related death in their careers. It is |


 

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|---|---|---|
| | | reasonable not to model any disease specific mortality. |
| Adverse events | Not included | Adverse event rates observed in the trial showed that no grade 3 or 4 AEs occurred in >5% of either treatment arm. There were no adverse events observed that were considered significant enough to be considered as part of the economic analysis. |
| Age adjusted utility | Included | The utility values for the patients within the economic analysis are adjusted with age throughout the time horizon. This is to account for the expected decline in background QoL as patients get older. This approach is representative of real-world setting. |

Abbreviations: AEs, adverse events; HAE, hereditary angioedema; NA, Not available; QoL, quality of life; SoC, standard of care; UK, United Kingdom


 

### *B.3.7 Base-case results*

Berotralstat generates [redacted] incremental QALYs for [redacted] incremental costs over a lifetime horizon compared with SoC, resulting in an ICER of £20,707 per QALY gained. Disaggregated base case results are presented in Appendix J.

**Table 39: Base-case incremental cost-effectiveness analysis results**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £20,707 | £20,707 |

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

## *B.3.8 Sensitivity analyses*

### B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitive analyses (PSA) was conducted to explore the impact of model parameters uncertainty on the results. PSA involves drawing a value at random for each variable from its uncertainty distribution. This is performed for each parameter simultaneously and the resulting incremental results are recorded. This constitutes one 'simulation'. 1,000 simulations were performed, which each gave a distribution of incremental results and an assessment of the robustness of the cost-effectiveness results.

For event rates and utilities, a beta distribution was used to restrict draws to between 0 and 1. For costs and resource use estimates, and hazard ratios a gamma distribution was fitted to prevent values less than zero. Treatment costs remained fixed. An incremental cost-effectiveness plane (ICEP) scatter plot and cost-effectiveness acceptability curve (CEAC) were produced to graphically illustrate the level of variability and uncertainty in the results.

The mean values for total costs, LYs, QALYs, and incremental cost per QALY gained for berotralstat versus SoC for the sub-population of interest generated through 1,000 simulations of the PSA are presented in Table 40. In the PSA, berotralstat generates [redacted] incremental QALYs and [redacted] incremental costs over a lifetime horizon compared with SoC, resulting in an ICER of £24,140 per QALY.

The corresponding ICEP and CEAC are presented in Figure 12 and


 

**Figure *13***, respectively. At a WTP threshold of £30,000 berotralstat had a [redacted] probability of being cost-effectiveness compared to SoC.

**Table 40: Mean PSA results**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | - | - | - |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | £24,140 |

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care

**Figure 12: Incremental cost effectiveness plane**


 

**Figure 13: Cost effectiveness acceptability curve**


 

### B.3.8.2 Deterministic sensitivity analysis

A deterministic one-way sensitivity analysis (OWSA) was conducted to explore the level of uncertainty in the model results. The OWSA involved varying one parameter at a time and assessing the subsequent impact on the incremental QALYs and incremental costs. By adjusting each parameter individually, the sensitivity of the model results to that parameter can be assessed.

The OWSA was conducted by allocating a 'low' value and a 'high' value to each parameter; the low value is the lower bound of the 95% confidence interval (CI), the high value is the upper bound of the 95% CI. The variable will be altered by +/- 20% in the absence of CI data. A tornado diagram was developed to graphically present the parameters which have the greatest effect on the ICER.

The OWSA tornado diagram presenting the top 15 most sensitive parameters for the sub-population of interest is presented in Figure 14. Table 41 presents the OSWA results for these 15 parameters. The model was most sensitive to the baseline attack rate for SoC, the proportion of attacks treated for SoC, and the price of berotralstat per cycle.


 

**Figure 14: Tornado diagram for the OWSA**

**Table 41: OWSA results for the 15 parameters that contribute the largest difference to the ICER**

| Parameter | Lower bound (£) ICER | Upper bound (£) ICER | Max Difference (£) ICER |
|---|---|---|---|
| Baseline attack rate (SoC) | £308,728 | -£161,170 | £288,021 |
| SoC: proportion of attacks treated | £238,990 | -£74,199 | £218,283 |
| Berotralstat price per cycle | -£170,816 | £212,229 | £191,522 |
| Berotralstat compliance | -£170,816 | £47,280 | £191,522 |
| Berotralstat: reduction of attack rate from baseline, from month 12 | £208,774 | -£123,676 | £188,067 |
| SoC: Firazyr cost per attack | £158,613 | -£117,199 | £137,906 |
| SoC: proportion of attacks treated with Firazyr single dose | £79,677 | -£38,263 | £58,970 |
| SoC: proportion of attacks treated with Firazyr single dose | £79,677 | -£38,263 | £58,970 |
| SoC: Berinert cost per attack | £58,673 | -£17,259 | £37,966 |
| SoC: proportion of patients requiring second dose of Firazyr | £57,853 | -£16,440 | £37,146 |
| SoC: proportion of attacks treated with Berinert single dose | £57,407 | -£15,993 | £36,700 |
| SoC: proportion of attacks treated with Berinert single dose | £57,407 | -£15,993 | £36,700 |
| Baseline attack rate (berotralstat) | -£9,938 | £52,981 | £32,274 |
| Patient weight (kg) | £51,920 | -£2,959 | £31,214 |
| Berotralstat: proportion of attacks treated | -£10,196 | £35,988 | £30,902 |

Abbreviations: ICER, incremental cost effectiveness ratio; kg, kilograms; SoC, standard of care

### B.3.8.3 Scenario analysis

Table 42 details scenario analyses results for berotralstat versus SoC for sub-population of interest. Results were most sensitive to varying the acute attack costs, the removal of the continuation rule, and adjustment of the acute therapy use based on UK clinical opinion.


 

**Table 42: Scenario analysis results**

| Parameter | Base case | Scenario setting | ICER (£/QALY) |
|---|---|---|---|
| Perspective | NHS and PSS | Societal | Berotralstat dominant |
| Time horizon | Lifetime (56 years) | 10 years | £41,740 |
| | | 20 years | £27,170 |
| Age | 44 years | 12 years | £18,054 |
| Continuation rule | Included | Excluded | £372,456 |
| Source of patient utility values | Nordenfelt et al. (2014) | TTO study | £27,248 |
| Administration disutilities | Excluded | Included | £16,422 |
| Use of acute treatment | Unadjusted APeX-2 data | APeX-2 data adjusted by UK clinical opinion | Berotralstat dominant |

Abbreviations: NHS, National Health Service; QALY, quality-adjusted life year

## *B.3.9 Subgroup analysis*

The population entering the economic analysis are a sub-population of the APeX-2 trial: patients experiencing ≥2 attacks per month and prior androgen use at baseline. Additionally, the attack rates for responding patients are used to inform the attack rates beyond month 3. No other sub-groups are used in the economic analysis.

## *B.3.10 Validation*

### B.3.10.1 Validation of cost-effectiveness analysis

Validation of the inputs and methodologies used within the economic analysis has been performed in a number of different ways:

- A Delphi panel process was used to generate consensus from UK clinicians for the parameters used to inform the continuation rule.[9]
- Resource use associated with attacks was informed by an advisory board featuring a number of UK clinicians. Participants were asked to validate a number of key modeling assumptions and to provide estimates for the resource use associated with attacks. The mean values of these estimates were used to inform the resource use parameters used within the economic analysis.
- The anticipated positioning of berotralstat within the treatment paradigm was validated by UK clinicians during the advisory board meeting. Complete consensus was established that the proposed positioning of berotralstat aligns with anticipated use of berotralstat in clinical practice as well as verifying that indicated population is the population of greatest unmet need.
- All key modeling assumptions have been validated by independent UK health economics experts.

## *B.3.11 Interpretation and conclusions of economic evidence*

Patients receiving berotralstat in the sub-population of interest accrued [redacted] QALYs at a cost of [redacted] over a lifetime time horizon. Over the same time horizon,


 

patients receiving SoC accrued [redacted] QALYs at a cost of £[redacted]. This results in a cost per QALY gained (ICER) of £20,707 per QALY. This value is below the willingness to pay threshold of £30,000 per QALY typically accepted by NICE.

[redacted]% of the probabilistic results fell below the £30,000 per QALY threshold, which demonstrates the robustness of the cost effectiveness of berotralstat despite variation of key input values. The OWSA results showed that the analysis was most sensitive to variation in baseline attack rate for SoC, the proportion of attacks treated for SoC patients, and the price of berotralstat.

Scenario analyses investigating adoption of a societal perspective, the inclusion of administration-based utilities, and adjusting the rate of acute therapy use based on the opinion of UK clinicians demonstrated an overall reduction in the ICER compared to the base case. Conversely, scenario analyses investigating reducing the time horizon, the exclusion of the continuation rule, and sourcing the utility values from the TTO study all resulted in an overall increase in the ICER.

The results of the base case analysis, probabilistic sensitivity analysis, and the majority of the scenario analyses indicate that berotralstat is a cost-effective use of NHS resources. The results show that the introduction of berotralstat into the treatment paradigm will significantly improve the QoL and provide a cost-effective use of NHS resources.

The economic analysis is relevant to all patients' groups who would benefit from the inclusion of berotralstat into the treatment paradigm due to the comparability of the patients entering the economic analysis and the indicated population who would benefit most from its inclusion.

The strengths of the analysis include:

- The clinical data used to inform the analysis was sourced from APeX-2, which included UK sites.
- All costs are source from relevant UK sources. This validates the estimated cost implications in UK clinical practice.


 

- Inputs of the economic analysis have been validated by UK clinicians. Again, this validates the estimated cost implications in UK clinical practice.

- The key assumptions of the analysis have been validated by independent UK-based health economists.

Potential weaknesses of the analysis include:

- Although the sample size of APeX-2 was relatively large for a rare disease such as HAE, it was necessary to utilise sub-groups of the trial population to align with the proposed positioning of berotralstat. Patient numbers informing the clinical data used in the economic analysis are small, and as such, the variation observed in a few patients drives the clinical measures in the economic analysis.

- Due to the nature of the condition and the structure of the trial, no representative EQ-5D data could be obtained from the trial population. However, it was possible to source relevant data from literature, which has previously been deemed appropriate for representing the HRQoL of HAE patients by NICE

- Attack location has been used as a proxy for attack severity to inform resource use associated with HAE attacks. However, as attacks in the same location may vary in severity, resource use may also vary. However, clinical experts agreed that certain resources were much more likely to be used for attacks in certain locations, in particular laryngeal attacks are associated with substantially higher resource use than attacks in other locations. Since attack location was more objectively defined than attack severity in APeX-2, it was decided that this was a more appropriate measure to use.


 

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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

## Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

## Clarification questions

**January 2021**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| ID1624 Berotralstat ERG Clarification letter to company v1.0 [ACIC] | V1.0 | Yes | 11.01.2021 |

**Notes for company**

**Highlighting in the template**

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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# Section A: Clarification on effectiveness data

## *Confidential information marking*

**A1. Section B.2.** Marking for confidential information has been used throughout the company submission. All information in the checklist of confidential information are coded as commercial in confidence. Please confirm this is the case and that there is no academic in confidence information in the clinical effectiveness sections of the submission.

Values on p19 and p71 in Document B, and p6 in Appendix L have now been redacted as academic in confidence. This has been reflected in the checklist of confidential information.

## *Risk of bias assessment*

**A2. Appendix D, Section D.7.** Please confirm whether risk of bias assessment was conducted by two or more reviewers independently.

The company can confirm that a risk of bias assessment was conducted by two or more reviewers independently. The risk of bias was initially assessed by one reviewer and validated by a second reviewer following the Cochrane Risk of Bias Tool for RCTs and the Newcastle-Ottawa Scale for non-RCTs. In 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. For the RCTs, the outcomes were the same for both the first and second assessment, thus confirming the results presented in the SLR report. For non-RCTs, all studies had the same overall rating in both the first and the secondment assessment. At a criteria level, all ratings were the same except for Zanichelli 2011, where the second reviewer set a lower grade for the "assessment of outcome" criteria. However, this had no impact on the overall score, since it was already deemed the lowest grade (poor quality) by the first reviewer.

**A3. Appendix D, Section D.7.** Please provide the results of the risk of bias assessment for each of the risk of bias domains, and overall risk of bias for the APeX-2 trial.

Detailed results from the risk of bias assessment of the APeX-2 trial are presented in Table 1 below.

**Table 1: Quality assessment for APeX-2**

| Bias Domain | | Details |
|---|---|---|
| **Selection Bias** | **Random sequence generation** | Enrollment into treatment groups was stratified by the interactive (web or voice) response system (IXRS) based on attack rate over the period between screening and randomization (≥ 2 attacks per month vs. < 2 attacks per month). |
| | **Allocation concealment** | Enrollment into treatment groups was stratified by the interactive (web or voice) response system (IXRS) based on attack rate over the period between screening and randomization (≥ 2 attacks per month vs. < 2 attacks per month).<br>Matching placebo was also provided as capsules to match the berotralstat capsules. The matching placebo contained microcrystalline cellulose. |
| | **Reviewer risk of bias assessment** | Low |
| **Performance Bias** | **Blinding of participants and personnel:** | Study drug assignment was blinded to the investigator, study staff, study subjects, and clinical research organization staff. Sponsor employee(s) were also blinded to the treatment allocation of individual subjects, with the exception of sponsor staff responsible for managing clinical supplies. Employees who were not blinded to drug assignment had no access to any other subject-level information for the duration of the study. |

| | | |
|---|---|---|
| | **Reviewer risk of bias assessment** | Low |
| **Detection Bias** | **Blinding of outcome assessment:** | Study drug assignment was blinded to the investigator, study staff, study subjects, and clinical research organization staff. Sponsor employee(s) were also blinded to the treatment allocation of individual subjects, with the exception of sponsor staff responsible for managing clinical supplies. Employees who were not blinded to drug assignment had no access to any other subject-level information for the duration of the study. |
| | **Reviewer risk of bias assessment** | Low |
| **Attrition bias** | **Incomplete outcome data** | Drop-outs were reported, and the reasons were mentioned |
| | **Reviewer risk of bias assessment** | Low |
| **Reporting Bias** | **Selective reporting** | All predefined outcomes were reported |
| | **Reviewer risk of bias assessment** | Low |
| **Other Bias** | **Other sources of bias** | All questions/entries pre-specified in the review protocol were addressed |
| | **Reviewer risk of bias assessment** | Low |

## *Characteristics of the APeX-2 trial*

**A4. Section B.2.3.3, Table 6 and Section B.2.6.3.** Table 11. Please provide the baseline AE-QOL scores for the berotralstat and placebo treatment arms of the APeX-2 trial.

The baseline AE-QoL scores for berotralstat and placebo treatment arms of the APeX-2 trial are detailed in Table 2 below. The baseline values reported are very similar with a mean AE-QoL score of [redacted] and [redacted] in the berotralstat 150mg arm and placebo arms, respectively.

**Table 2: Summary of AE-QoL Baseline Scores (ITT Population)**

| | [redacted] | [redacted] |
|---|---|---|
| AE-QoL total score | | |
| N | [redacted] | [redacted] |
| Mean (SD) | [redacted] | [redacted] |
| Median | [redacted] | [redacted] |
| Range | [redacted] | [redacted] |

Abbreviations: AE-QoL, Angioedema Quality of Life; ITT, intent to treat; N, number of patients

## *Statistical analyses and clinical effectiveness results*

**A5. Section B.2.4, Table 7** The summary of statistical analyses table shows that the stratification variable (baseline attack rate) was included as a covariate. Please clarify if this was entered as a continuous or categorical variable.

The stratification variable (baseline attack rate) was entered as a continuous variable.

**A6. Section B.2.6.1, Table 8.** Please clarify if the presented rates per 28 days in this table are mean values related to the participants in each arm of the trial. If so, please provide the standard deviations of these means.

These are not mean values, they are estimated attack rates from the negative binomial model, and as such, no standard deviations are available.

**A7. Section B.2.6.1, Tables 8 and 9.** Please clarify why the mean attack rate per 28 days for berotralstat 150mg of 1.31 reported in table 8 (if it is indeed a mean) is lower than all the observed monthly mean rates for berotralstat presented in Table 9.

The values in Table 8 are not mean values, they are estimated attack rates from the negative binomial model and therefore are not comparable to the means presented in Table 9.

Table 8 uses a statistical model (negative binomial model) that looks at the attack rate over Part 1 (Day 1-Week 24). It uses the negative binomial model with baseline attack rate as a covariate. It includes the duration of treatment as an offset variable. Table 9 is straight means by month. Although they are not the same, the primary comparison of interest is the Table 8 comparison of placebo to berotralstat 150mg.

Comparisons in Table 9 also show lower attack rates for berotralstat 150mg compared to placebo.

# Section B: Clarification on cost-effectiveness data

## *Clinical parameters and variables*

**B1. Document B, Section B.3.3.** In the subgroup used in the economic model (n=35), please clarify how many patients received berotralstat and how many received SoC.

The subgroup consisted of 17 berotralstat patients and 18 SoC patients.

**B2. Document B, Section B.3.3.1, Table 21.** Please provide the baseline demographics separately for the berotralstat and SoC arms.

The baseline demographics for the berotralstat and placebo treatment arms for patients with ≥2 attacks per month and prior androgen use at baseline in the APeX-2 trial are detailed in Table 3 below.

**Table 3: Baseline demographics for subgroup of patients**

| Baseline demographics | Berotralstat | SoC |
|---|---|---|
| Mean age | [redacted] | [redacted] |
| Percentage female | [redacted] | [redacted] |
| Mean weight (kg) | [redacted] | [redacted] |

Abbreviations: SoC, standard of care; kg, kilograms

**B3. Document B, Section B.3.3.2.** Please clarify how many patients in the subgroup met the criteria for continuation resulting in the [redacted] response rate.

[redacted] berotralstat patients experienced a ≥50% reduction in attack rate compared to baseline at three months and therefore met the criteria for continuation.

**B4. PRIORITY. Document B, Section B.3.3.4, Table 26.** In relation to the attack rate applied beyond 6 months in the SoC arm and beyond 12 months in the berotralstat arm, please provide a sensitivity analysis using the mean attack rate

from month 0-6 for SoC and for 4-12 months for berotralstat instead of using the last observation carried forward (LOCF) approach.

The company believes that the use of LOCF to estimate attack rates beyond the time horizon of the APeX-2 trial is valid and appropriate statistical methodology. Whilst the use of an average of attack rates may also be a valid methodology, in this case the company does not believe it is appropriate.

As shown in Figure 1, the attack rate within the SoC patients subgroup in APeX-2 decreased in the months following the start of the trial, before increasing once more as participation in the placebo group came to an end. During Month 2 and Month 3, SoC patients experienced a [redacted] reduction in attack rate from baseline. It is clinically implausible that such a reduction would normally be observed in patients not receiving active prophylactic treatment. It seems more likely that these patients experienced a placebo effect early in the trial, which then disappeared by Month 6.

[redacted]

[redacted]

In UK clinical practice, patients in the subpopulation of interest who are not treated with berotralstat would not receive any placebo and as such would be dependent on acute treatment at attack onset. They would therefore not experience any placebo effect, as observed in the APeX-2 trial.

Using an average attack rate for months 0-6 of the placebo arm of the subgroup of interest in the economic model would skew the data in favour of this placebo effect and does not reflect the effect that patients would experience in UK clinical reality, where it is more likely their attack rate would remain the same or even increase. As such, the use of LOCF was deemed more realistic than using an average attack rate.

Therefore, the company believes that the LOCF methodology is the most appropriate but has also provided two scenarios below that capture alternative methodologies.

In the first scenario, the baseline attack rate for SoC is applied as the attack rate throughout the time horizon of the economic model, so that no placebo effect is applied. The berotralstat attack rate beyond month 12 uses an average of the mean attack rates observed in months 4-12, weighted by the number of patients contributing data at each time point. Berotralstat generates [redacted] over a lifetime horizon compared with SoC, resulting in a an ICER of [redacted] gained.

**Table 4: B4 Sensitivity analysis (Berotralstat mean attack rate, SoC baseline attack rate applied thoughout) - incremental-cost-effectiveness results**

| | Berotralstat | SoC |
|---|---|---|
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |

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

In the second scenario, as requested by the ERG, the average attack rates for SoC and berotralstat in months 0-6 and 4-12 respectively, weighted by the number of patients contributing data at each time point, are applied beyond the time horizon of the trial. Berotralstat generates [redacted] over a lifetime horizon compared with SoC, resulting in a an ICER of [redacted] gained. As mentioned above, the company believes that

this is not a clinically plausible scenario due to the absence of the placebo effect in months 0-6.

**Table 5: B4 Sensitivity analysis - incremental-cost-effectiveness results**

| | Berotralstat | SoC |
|---|---|---|
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |

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

**B5. PRIORITY. Document B, Section B.3.3.4, Table 22.** Please provide sensitivity analysis using the pooled baseline attack rate in both arms instead of applying attack rates by patient arm as outlined in this table**.**

When a pooled baseline attack rate is applied in both arms, berotralstat generates [redacted] over a lifetime horizon compared with SoC, resulting in a [redacted] for berotralstat.

**Table 6: B5 Sensitivity analysis - incremental-cost-effectiveness results**

| | Berotralstat | SoC |
|---|---|---|
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |

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

**B6. Document B, Section B.3.3.4. Table 23.** Please provide the corresponding numbers of patients and numbers of attacks for the data reported by treatment arm and month in this table.

The number of patients and mean numbers of attacks by treatment arm and month are detailed in Table 7 below.

**Table 7: Mean number of attacks per month from baseline to month 6 for patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| Treatment | Mean number of attacks | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | Month 1 | | Month 2 | | Month 3 | | Month 4 | | Month 5 | | Month 6 | |
| | n | Mean | n | Mean | n | Mean | n | Mean | n | Mean | n | Mean | n | Mean |
| Berotralstat | [redacted] | | | | | | | | | | | | | |
| SoC | [redacted] | | | | | | | | | | | | | |

Abbreviations: SoC, standard of care

**B7. Document B, Section B.3.3.4. Table 24.** Please provide the corresponding numbers of patients and numbers of attacks for the data reported by month in this table.

The number of patients and numbers of attacks by treatment arm and month are detailed in Table 8 below.

**Table 8: Mean number of attacks per month from month 7 to month 12 for patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| Treatment | Mean number of attacks | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Month 7 | | Month 8 | | Month 9 | | Month 10 | | Month 11 | | Month 12 | |
| | n | Mean | n | Mean | n | Mean | n | Mean | n | Mean | n | Mean |
| Berotralstat | [redacted] | | | | | | | | | | | |

**B8. PRIORITY. Document B, Section B.3.3.4. Table 25.** Please provide:

a) The baseline and month 1, 2 and 3 attack rates for this subgroup of responders;

b) The percentage change in the number of attacks from baseline for this smaller subgroup of responders;

c) the corresponding numbers of patients and numbers of attacks for the data reported by month;

d) a cost-effectiveness scenario analysis whereby the percentage reductions from baseline for responders are calculated using the baseline attack rate for this restricted group of responders, not the average for the larger subgroup.

a) The baseline and month 1, 2, and 3, attack rates for this subgroup of responders are detailed in Table 9 below.

**Table 9: Mean number of attacks per month from baseline to month 3 for responder patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| | Mean number of attack rates | | | |
|---|---|---|---|---|
| | **Baseline** | **Month 1** | **Month 2** | **Month 3** |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] |

b) The percentage change in the number of attacks for this subgroup of responders is detailed in Table 10 below.

**Table 10: Percentage change from baseline to mean attack rate for responder patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| | Percentage change from baseline (%) | | | |
|---|---|---|---|---|
| | **Baseline** | **Month 1** | **Month 2** | **Month 3** |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] |

c) The number of patients alongside the mean number of attack rates is presented below in Table 11 for this subgroup of responders.

The rates for months 4 and 5 were unfortunately reported incorrectly in the company submission. The standard deviation values were erroneously reported instead of the mean values. The correct values for months 4 and 5 are reported below in Table 11.

**Table 11: Number of patients and mean attack rate per month for responder patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| | Berotralstat | |
|---|---|---|
| | **n** | **Mean attack rate** |
| Baseline | [redacted] | [redacted] |
| Month 1 | [redacted] | [redacted] |
| Month 2 | [redacted] | [redacted] |
| Month 3 | [redacted] | [redacted] |
| Month 4 | [redacted] | [redacted] |
| Month 5 | [redacted] | [redacted] |
| Month 6 | [redacted] | [redacted] |
| Month 7 | [redacted] | [redacted] |
| Month 8 | [redacted] | [redacted] |
| Month 9 | [redacted] | [redacted] |
| Month 10 | [redacted] | [redacted] |
| Month 11 | [redacted] | [redacted] |
| Month 12 | [redacted] | [redacted] |

d) A scenario analysis has been applied where the baseline attack rate used in the model is that of the smaller subgroup of responders. In this scenario, berotralstat generates [redacted] over a lifetime horizon compared with SoC, resulting in an ICER of [redacted]

**Table 12: B8(d) Scenario analysis (responder baseline attack rate and reductions applied) - incremental-cost-effectiveness results**

| | Berotralstat | SoC |
|---|---|---|
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |

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

**B9. Document B, Section B.3.3.5. Table 27.** Please provide the corresponding number of patients and number of attacks for the data reported in this table.

The number of patients and numbers of attacks by treatment arm are detailed in Table 13 below.

**Table 13: Location of attacks observed in the APeX trials for patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| Attack location | Total number of attacks | |
|---|---|---|
| | Berotralstat; N=17 | SoC; N=18 |
| Abdominal/thoracic | [redacted] | [redacted] |
| Limb/other | [redacted] | [redacted] |
| Laryngeal | [redacted] | [redacted] |

Abbreviations: SoC, standard of care

**B11. Document B, Section 3.4.5.** Please provide sensitivity analysis removing the caregiver disutility associated with an attack.

As described in Section B.1 of the company submission, there is a significant burden experienced by caregivers of HAE patients due to the substantial amount of time spent offering both physical and emotional support as well as shared anxiety over attacks. This burden also includes limitations to educational and employment opportunities.

Furthermore, it is also within the remit of NICE to consider caregiver burden, with the reference case stating that *'all direct health effects, whether for patients or, when relevant, carers'* should be considered.

As such, we believe it is inappropriate to model the effects of HAE without taking caregiver burden into account. However, in line with the ERG's request we have provided the scenario below.

When caregiver disutility associated with an attack is removed, berotralstat generates [redacted] over a lifetime horizon compared with SoC, resulting in an ICER of [redacted]

**Table 14: B11 Sensitivity analysis (caregiver disutility excluded) - incremental-cost-effectiveness results**

| | Berotralstat | SoC |
|---|---|---|
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |

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

**B10. Document B, Section B.3.3.6. Table 28.** Please provide the number of patients, number of attacks and duration for each type of attack (abdominal/thoracic limb or other, and laryngeal).

The number of patients, numbers of attacks and duration for each type of attack by treatment arm are detailed in Table 15 below.

**Table 15: Mean attack duration for patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| Variable | Berotralstat | SoC |
|---|---|---|
| Abdominal/thoracic | | |
| Number of attacks | [redacted] | [redacted] |
| Mean duration (hours) | [redacted] | [redacted] |
| Limb or other | | |
| Number of attacks | [redacted] | [redacted] |
| Mean duration (hours) | [redacted] | [redacted] |
| Laryngeal | | |
| Number of attacks | [redacted] | [redacted] |
| Mean duration (hours) | [redacted] | [redacted] |

Abbreviations: SoC, standard of care

## *Measurement and valuation of health effects*

**B12. Document B, Section B.2.6.4 and Section B.3.4.1.** Please provide more details on the EQ-5D data collected in the APeX-2 trial, such as the number of

observations at each time point, mean EQ-5D score at each time point and any information on the number of EQ-5D responses that coincided with an attack.

EQ-5D scores for patients with ≥2 attacks per month and prior androgen use at baseline of APeX-2 are presented in Table 16, split by whether or not an attack was ongoing at the time of assessment. An attack was defined as ongoing if it began ≤2 days prior to the assessment.

As stated in the company submission, the company considers that EQ-5D data is not suitable to characterise either 'attack' or 'attack-free' utility values in the economic model.

The patient numbers for whom an attack is ongoing is too small to allow for interpretation at several timepoints and gives very unrealistic results. For example, at Week 12, SoC patients are recorded as having a perfect utility value of 1 while experiencing an attack, which is not clinically plausible.

For patients who were not experiencing an attack at the time of assessment the utility values produced are unrealistic. The following formula was used to calculate age-adjusted utility values for the general population:[1]

$$General\ population\ utility = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$$

The age-adjusted utility value for a member of the general population with the same demographics as the subgroup of interest of APeX-2 was calculated as [redacted] which is lower than many of the values observed for attack-free HAE patients in APeX-2. It is not clinically plausible that an HAE patient, even when attack-free, would have better quality of life than a member of the general population. As such, the utility values recorded in APeX-2 do not accurately capture the HRQoL of patients with HAE and should not be used to characterise it in the economic model, particularly when other more targeted HAE specific data is available from other sources.

**Table 16: Detailed EQ-5D data from APeX-2**

| 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

The adverse event profile (Table 17) of berotralstat further discredits these unusual scores. The overall summary of TEAEs for the ITT population is reported below. No patient in the berotralstat 150 mg group experienced a treatment-emergent SAE or a drug-related Grade 3 or 4 TEAE. All study drug related TEAEs were mild to moderate and only one berotralstat patient discontinued the drug due to a TEAE. It is anticipated that even lower rates would be observed in the subgroup of interest. Given these low rates, AE disutility cannot explain why the SoC arm produces higher utility values than berotralstat further emphasising why the EQ-5D values obtained in APeX-2 are inappropriate for use in the economic model.

**Table 17: Overall Summary of TEAEs (Safety Population)**

| **TEAE Summary** | **Berotralstat 150 mg; N=40 n (%)** | **Placebo; N=39 n (%)** |
|---|---|---|
| Number of patients with: | | |
| Any TEAE | 34 (85.0%) | 30 (76.9%) |
| Any drug-related TEAE[a] | 15 (37.5%) | 13 (33.3%) |
| Any SAE | 0 | 3 (7.7%) |
| Any drug-related SAE | 0 | 0 |
| Any Grade 3 or 4 TEAE | [redacted] | [redacted] |
| Any drug-related Grade 3 or 4 TEAE | 0 | 0 |
| Any TEAE leading to interruption of study drug[b] | [redacted] | [redacted] |

| | | |
|---|---|---|
| Any TEAE leading to discontinuation of study drug | 1 (2.5%) | 1 (2.6%) |
| Any investigator-identified rash[c] | 1 (2.5%) | 0 |
| Any GI abdominal TEAE[d] | 20 (50.0%) | 14 (35.9%) |
| Any GI abdominal TEAE leading to discontinuation of study drug | 0 | 0 |
| Notes: A drug-related TEAE was defined as any AE where the investigator defines the relationship to blinded study drug as Possibly Related, Probably Related, or Definitely Related. b An AE leading to interruption of study drug was any AE where the Action Taken on the AE eCRF was marked as 'Drug Interrupted'. c An investigator-identified rash was any AE that the investigator noted as an AE of special interest on the AE eCRF. d GI abdominal AE was any AE with a PT within the MedDRA 19.1 hierarchy under the High-level Group Terms of 1) GI signs and symptoms or 2) GI motility and defaecation conditions. | | |

Abbreviations: AE, adverse event; eCRF, electronic case report form; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; n, number of patients who experienced the event; PT, preferred term; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

**B13. Document B, Section 3.4.1.** Please provide a sensitivity analysis using the EQ-5D data from the APeX-2 trial for the 'attack free' health state.

A weighted average of EQ-5D scores at baseline and all further timepoints for patients for whom an attack was not ongoing at the time of assessment was applied to 'attack-free' patients in the economic model.

When the same utility score (0.911) is applied to berotralstat and SoC patients in the model, berotralstat generates [redacted] over a lifetime horizon compared with SoC, resulting in an ICER of [redacted] per QALY gained.

**Table 18: B13 Sensitivity analysis (attack-free EQ-5D) - incremental-cost-effectiveness results**

| | Berotralstat | SoC |
|---|---|---|
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |

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

**B14. Document B, Section B.3.5.1. Table 31**. Please provide the corresponding number of patients and number of attacks for the data reported in this table.

The number of patients and number of attacks treated with acute therapy is detailed in Table 19.

**Table 19: Administration of acute therapies observed in APeX-2 for patients experiencing ≥2 attacks per month and previous use of androgens at baseline**

| Variable | Berotralstat; N=17 | SoC; N=18 |
|---|---|---|
| *Attacks treated* | | |
| Number of attacks treated with any acute therapy | [redacted] | [redacted] |
| *Attacks treated with a single dose of acute treatment* | | |
| Number treated with:<br>• Berinert: 1 dose | [redacted] | [redacted] |
| Number treated with:<br>• Cinryze: 1 dose | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 1 dose | [redacted] | [redacted] |
| Number treated with:<br>• Ruconest: 1 dose | [redacted] | [redacted] |
| *Attacks treated with multiple doses of acute treatment* | | |
| Number treated with:<br>• Berinert: 1 dose<br>• Cinryze: 1 dose | [redacted] | [redacted] |
| Number treated with:<br>• Berinert: 1 dose<br>• Firazyr: 1 dose | [redacted] | [redacted] |
| Number treated with:<br>• Cinryze: 1 dose<br>• Firazyr: 1 dose | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 1 dose<br>• Ruconest: 1 dose | [redacted] | [redacted] |
| Number treated with:<br>• Cinryze: 2 doses | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 2 doses | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 2 doses<br>• Berinert: 1 dose | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 2 doses<br>• Cinryze: 1 dose | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 2 doses<br>• Ruconest: 1 dose | [redacted] | [redacted] |

| | | |
|---|---|---|
| Number treated with:<br>• Ruconest: 2 doses<br>• Cinryze: 1 dose | [redacted] | [redacted] |
| Number treated with:<br>• Cinryze: 3 doses | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 3 doses | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 3 doses<br>• Berinert: 1 dose | [redacted] | [redacted] |
| Number treated with:<br>• Cinryze: 4 doses | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 4 doses | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 4 doses<br>• Berinert: 1 dose | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 5 doses | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 5 doses<br>• Berinert: 1 dose | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 5 doses<br>• Berinert: 2 doses | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 6 doses | [redacted] | [redacted] |
| Number treated with:<br>• Firazyr: 7 doses | [redacted] | [redacted] |
| Number treated with:<br>Firazyr: 10 doses | [redacted] | [redacted] |

## *Resource use and costs*

**B15. Document B, B.3.5.1.** For weight-based dosing of berinert, it is stated that the mean weight of patients in Apex-2 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. Please provide this as a scenario analysis.

Within the subgroup of interest for this submission, 11 patients received acute treatment with Berinert with Part 1 of APeX-2. The weight of each patient was recorded at baseline, and for the purposes of this analysis was assumed to be constant throughout the trial period. Two pack sizes of Berinert, 1500IU and 500IU, were used,

at a cost of £1,650 and £550 per pack, respectively. The recommended dose of 20IU/kg per administration was used. As in the base case analysis, a conservative assumption not to account for treatment wastage was applied.

Table 20 shows the data required to calculate the average cost per administration of Berinert, when individual weights are used instead of a single average weight.

**Table 20: Cost per administration of Berinert**

| Patient number | Weight (kg) | Dose (IU) | Unit size | Number of packs required | Cost per administration (£) |
|---|---|---|---|---|---|
| 1 | [redacted] | [redacted] | 1500 IU | £1,650 | [redacted] |
| | | | 500 IU | £550 | |
| 2 | [redacted] | [redacted] | 1500 IU | £1,650 | [redacted] |
| | | | 500 IU | £550 | |
| 3 | [redacted] | [redacted] | 1500 IU | £1,650 | [redacted] |
| | | | 500 IU | £550 | |
| 4 | [redacted] | [redacted] | 1500 IU | £1,650 | [redacted] |
| | | | 500 IU | £550 | |
| 5 | [redacted] | [redacted] | 1500 IU | £1,650 | [redacted] |
| | | | 500 IU | £550 | |
| 6 | [redacted] | [redacted] | 1500 IU | £1,650 | [redacted] |
| | | | 500 IU | £550 | |
| 7 | [redacted] | [redacted] | 1500 IU | £1,650 | [redacted] |
| | | | 500 IU | £550 | |
| 8 | [redacted] | [redacted] | 1500 IU | £1,650 | [redacted] |
| | | | 500 IU | £550 | |
| 9 | [redacted] | [redacted] | 1500 IU | £1,650 | [redacted] |
| | | | 500 IU | £550 | |
| 10 | [redacted] | [redacted] | 1500 IU | £1,650 | [redacted] |
| | | | 500 IU | £550 | |
| 11 | [redacted] | [redacted] | 1500 IU | £1,650 | [redacted] |
| | | | 500 IU | £550 | |

Therefore, the average cost per administration of Berinert was £1,843.89. This cost was applied every time Berinert is used in the model, and was repeated when multiple administrations were applied based on APeX-2 data.

This approach generates [redacted] over a lifetime horizon for berotralstat compared with SoC, resulting in an ICER of [redacted]

**Table 21: B15 scenario analysis (individual berinert dosing applied) – incremental cost-effectiveness results**

| | Berotralstat | SoC |
|---|---|---|
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |

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

## *Sensitivity analyses*

**B16. Company model, "Clinical Inputs".** The probabilistic sensitivity analysis uses 10% of the mean to represent the standard error for percentage reductions in attack frequency from baseline. Please calculate the actual standard errors from the trial data for application in the PSA.

When actual standard errors are applied in the probabilistic sensitivity analysis for percentage reductions in attack frequency, berotralstat generates [redacted] over a lifetime horizon compared with SoC, resulting in an ICER of [redacted] gained.

**Table 22: B16 Sensitivity analysis (actual standard errors) - incremental-cost-effectiveness results**

| | Berotralstat | SoC |
|---|---|---|
| Total costs (£) | [redacted] | [redacted] |

| | | |
|---|---|---|
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |

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

The company recognises that it is important to capture the true variability of the inputs within the economic model to best understand the impact of the level of uncertainty. However, 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.

The magnitude of the standard errors calculated for the attack rates in the trial population are directly linked to the sample size. The subgroup of APeX-2 used to estimate the attack rates per cycle contained a relatively small number of patients. For this reason, the estimated standard errors are too large to reflect the relative uncertainty of the attack rate estimates. 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.

The percentage reduction in attack rate is restricted to a maximum of a reduction of 100%. With many of the estimates for reduction in attack rate for the berotralstat patients being close to a reduction of 100%, extreme variation in increasing the level of reduction is limited to a maximum of 100% whereas extreme variation reducing the level of reduction allows for values close to 0% to be realistic. When estimates are drawn from the sampling distribution repeatedly as part of the PSA, this leads to a skewness which results in more 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. When averaged over the 1000 iteration of the PSA this effect introduces a level of bias in favour of SoC which has the result of increasing the ICER observed on average.

**B17. Document B, Section B.3.8.3, page 118.** The Company Submission states that results were most sensitive to varying the acute attack costs, but the result of this analysis is not provided in the scenario analyses results table (Table 42). Please provide these results and details of the alternative scenarios used.

As stated in the company submission, the use of acute treatment was based on RCT data from APeX-2, which is the gold-standard for resource use data. The use of medical resources was sourced from an advisory board meeting at which eight UK clinical experts came to a consensus on the frequency of the use of these resources. As such, the costs associated with acute attacks in the economic model are robust and accurate. However, the company has provided the below scenario demonstrating the economic impact of varying the costs associated with acute attacks.

When acute attack costs are increased by +10%, berotralstat [redacted] over a lifetime horizon compared with SoC, resulting in a [redacted] for berotralstat.

When acute attack costs are decreased by -10%, berotralstat generates berotralstat [redacted] over a lifetime horizon compared with SoC, resulting in an ICER of [redacted]

**Table 23: B17 scenario analysis (acute attack costs) – incremental cost-effectiveness results**

| | Berotralstat | SoC |
|---|---|---|
| **Acute costs +10%** | | |
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |
| **Acute costs -10%** | | |
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |

| | | |
|---|---|---|
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |

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

**B18. Document B, Appendix L, Section L.1.** Please provide results for the treatment waning scenario analyses in which the effect of treatment waning occurs at 5, 10 and 20 years**.**

The Company would like to highlight that whilst this ERG request has been completed, they do not think that this scenario is appropriate given the available evidence. As highlighted throughout the submission, long term data from APeX-2 indicates that the treatment effect of berotralstat is sustained over time, with no waning effect observed. Figure 2 and

[redacted] show the most recent long-term data for the mean attack rates per month for responder patients in the subgroup of interest. See Appendix A for the figures including patients who transitioned from placebo to berotralstat following Part 1 of APeX-2.

[redacted]

[redacted]

It is clear from these figures that no waning effect is observed after 24 months of treatment, and as such it is unrealistic to assume that the treatment effect of berotralstat would wane entirely, especially in a time period as short as 5 or 10 years.

However, we have conducted analyses as requested, where a 100% reduction in treatment effect due to treatment waning leading to treatment discontinuation at each time horizon (5, 10, 20 years).

The analysis shows that when treatment waning occurs at 5 years, [redacted] over a life time horizon for berotralstat compared with SoC, resulting in an ICER of [redacted]

The ICER decreases as the time horizon for treatment waning increases. The resulting ICER at 10 years treatment waning is [redacted] and at 20 years treatment waning this is [redacted]

**Table 24: B18 Scenario analyses (treatment waning) – incremental cost-effectiveness results**

| | Berotralstat | SoC |
|---|---|---|
| **Treatment waning: 5 years** | | |
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |
| **Treatment waning: 10 years** | | |
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |

| | | |
|---|---|---|
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |
| **Treatment waning: 20 years** | | |
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |

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

**B19. Document B, Appendix L, Section L.2. Time trade-off study.** "*Participants were then asked to imagine that they suffered with the condition described in each of the six health states shown in Table 5*". Please provide Table 5. In addition, please provide the TTO questionnaire including wording for the vignettes and questions asked**.**

The correct text is as follows: "*Participants were then asked to imagine that they suffered with the condition described in each of the six health states shown in Table 1*".

The content of *Table 1* is provided in Table 25 below.

**Table 25: TTO ratings for patients and caregiver HAE health state vignettes (N=100)**

| Health State | Mean (SD) | SE | 95% CI |
|---|---|---|---|
| P1: attack free state | [redacted] | [redacted] | [redacted] |
| P2: abdominal attack state | [redacted] | [redacted] | [redacted] |
| P3: facial attack state | [redacted] | [redacted] | [redacted] |
| P4: hand attack state | [redacted] | [redacted] | [redacted] |
| P5: laryngeal attack state | [redacted] | [redacted] | [redacted] |
| Caregiver state | [redacted] | [redacted] | [redacted] |

Abbreviations: CI, confidence interval SD, standard deviation; SE, standard error; TTO, time trade-off

The TTO questionnaire including wording for the vignettes and questions asked is presented in References

Ara R, & Brazier JE. Populating an economic model with health state utility values: moving toward better practice. 2010. 13(5):509-18

Appendix A.

**B20. Document B, Appendix L, Section L.2. Time trade-off study.** Please provide number of participants for the TTO study. In addition, please provide participant numbers for the Mean (SD) values reported in *Table 1: TTO ratings for patients and caregiver HAE health state vignettes***.**

The TTO study included 100 participants. This also applies to the participant numbers in Table 1 in Appendix L.

**B21. Document B, Section 3.5.2 and Appendix L, Section L.4.** Please provide further details for the clinicians participating in the advisory board meeting on 2nd November 2020, such as number of participants and expertise**.**

Eight UK clinical experts attended the advisory board meeting on 2nd November 2020. Details of their expertise are provided below:

[redacted]

**B22. <u>PRIORITY</u>.** Given the very small numbers of patients in the subgroups used to inform the economic model, and a lack of evidence to support previous experience of androgens or baseline attack frequency as effect modifiers, please provide a scenario analysis 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). Please also provide scenario analyses that combine these changes with those requested in questions B4, B8 (d).

The Company would like to highlight that whilst the ERG request has been completed (Table 26), they do not consider this scenario to be clinically appropriate.

The Company reiterates 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, and the population where physicians anticipate most benefit from treatment: patients with ≥2 clinically significant attacks per month and who are unsuitable or refractory to androgens.

The subgroup of patients with ≥2 clinically significant attacks per month and who are unsuitable or refractory to androgens has been identified, in both the advisory board (see response to B.21 for clinician details) and Delphi panel with UK HAE clinicians, as the patient group with the most unmet need under current UK clinical practice. The proposed positioning of berotralstat has been selected based upon this unmet need. Patients with ≥2 attacks per month at baseline have a more severe form of HAE and experience a much greater impact to their quality of life and daily activities than patients who experience fewer attacks, and as such have a greater unmet need and would benefit more from treatment. Current routine prophylaxis therapies are only available for patients with ≥2 attacks per week, heightening the unmet need for the majority of patients with ≥2 attacks per month. The proposed positioning of berotralstat has been selected based upon this unmet need.

Patients experiencing <2 attacks per month would be very unlikely to receive berotralstat in UK clinical practice according to UK clinical expert opinion from an advisory board and Delphi panel, and therefore using clinical data pertaining to these patients will bias the cost-effectiveness assessment of berotralstat.

Furthermore, it is anticipated that patients will have already received treatment with androgens and discontinued prior to being treated with berotralstat, as the proposed positioning of berotralstat is for patients who are unsuitable or refractory to androgens. Using the ITT population of APeX-2 to inform the economic model would mean including patients who would be very unlikely to receive berotralstat in UK clinical practice. This is inappropriate and undermines the cost-effectiveness

evidence that will be used for decision-making. Therefore, it is inappropriate to use clinical data including these patients as the basis for decision-making for berotrastat.

Due to the rare nature of HAE, it is typical that there are small patient numbers in clinical trials. However, the subgroup used to inform the economic analysis (i.e patients with ≥2 attacks at baseline and prior androgen) still comprises [redacted] of the ITT population, which is not insignificant, and this should not be used to discount the validity of the evidence.

Therefore the company does not believe it is appropriate to present a scenario analysis using the ITT population from APeX-2. However, to address the request by the ERG scenarios have instead been provided in which patients with ≥2 attacks per month at baseline are included, with no limitations on prior androgen use, despite this not aligning with the proposed positioning of berotralstat in the UK.

In both the ITT population and the subgroup of patients with ≥2 attacks per month at baseline, the placebo effect experienced by patients in the SOC arm is even more pronounced than in the subgroup of patients with ≥2 attacks per month at baseline and prior androgen use (see response to B.4). The average reduction from baseline in the ITT population SOC arm over months 0-6 is [redacted]% in both groups, with a peak [redacted]% reduction in attack rate observed in month 5 for patients with ≥2 attacks per month at baseline. It is unrealistic that patients would experience such reductions in attack rates in clinical practice without receiving active treatment. The company believes it is more appropriate to use the baseline attack rate for SoC patients throughout the model time horizon, and a scenario has been presented to this effect below in Table 26.

**Table 26: B22 Scenario analyses – incremental cost-effectiveness results**

| | Berotralstat | SoC |
|---|---|---|
| **B22 (≥2 attacks per month)** | | |
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |

| | | |
|---|---|---|
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |
| **Alternative B22 (≥2 attacks per month, SoC baseline attack rate applied thoughout)** | | |
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |
| **B22 & B4 (≥2 attacks per month; berotralstat mean attack rate, SoC baseline attack rate applied thoughout)** | | |
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |
| **B22 & B8d (≥2 attacks per month; responder baseline attack rate applied)** | | |
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |

## Section C: Textual clarification and additional points

None

# Section D: Scenario Analyses

**Table 27: Summary of ERG requested scenarios**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| **B4 (SoC baseline attack rate applied thoughout)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B4 (average attack rates applied)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B5 (pooled attack rate)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B8d (responder baseline attack rate and reductions applied)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B11 (caregiver disutility excluded)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B13 (attack-free EQ-5D)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B15 (individual berinert administration applied)** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **B16 (actual standard errors)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **B17 (Acute costs +10%)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **B17 (Acute costs -10%)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **B18 (Treatment waning: 5 years)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **B18 (Treatment waning: 10 years)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **B18 (Treatment waning: 20 years)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **B22 (≥2 attacks per month)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **Alternative B22 (≥2 attacks per month, SoC attack reduction set to 0%)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **B22 & B4 (≥2 attacks per month; berotralstat mean attack rate, SoC baseline attack rate applied thoughout)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B22 & B8d (≥2 attacks per month; responder baseline attack rate applied)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

## References

1. Ara R, & Brazier JE. Populating an economic model with health state utility values: moving toward better practice. 2010. 13(5):509-18

# Appendix A

## B18 – Attack rates up to month 24, all treatment arms

Figure 4 and Figure 5 and show the most recent long-term data from APeX-2 for the mean attack rates per month for responder patients in the subgroup of interest.

[redacted]

[redacted]

## B19 - Final health state vignettes

### Patient State 1

- You have a life-long incurable condition which sometimes causes swelling in different body parts. Swelling can be suddenly brought on by known or unknown triggers.
- ***Currently***, you ***do not have any*** swelling.
- Your mobility and physical function are normal for someone your age.
- You are able to wash and dress normally.
- You are able to go about daily activities such as work/school, housework, childcare and social activities.
- You have some scars from injections you need to have because of your condition.
- You need to remember to take your injection, various items to administer the injection, and other medication with you wherever you go. You need to plan ahead to make sure there is a suitable space for you to take the medication if you have swelling. You may also need to plan where you could get emergency hospital care if necessary.
- You avoid activities that could trigger swelling, such as carrying heavy objects, strenuous/contact sports or repetitive movements. Stressful situations can also trigger a swelling.
- You have adapted your lifestyle because of your condition.
- You sometimes feel tired and sometimes have difficulties sleeping.
- You sometimes feel down or depressed. You often feel afraid or anxious about experiencing sudden swelling. If affecting your throat, it can obstruct your breathing, which could be fatal.

### Patient State 2

- You have a life-long incurable condition which sometimes causes swelling in different body parts. Swelling can be suddenly brought on by known or unknown triggers.
- You ***currently have*** swelling in your ***tummy*** causing you to experience cramps and severe pain. Symptoms may also include diarrhoea, nausea and vomiting.
- Your mobility and physical function are limited by your swelling and the severe pain you experience.
- You find it difficult to wash and dress yourself because of pain and tiredness.
- You have a lack of appetite.
- You are unable to leave your home and need to rest in bed most of the time because of your swelling. You might need to go to hospital, if the swelling is not controlled.
- You are unable to go about daily activities, such as work/school, housework, childcare and social activities.
- You feel dependent on your partner/family for help around the house and for care for your child(ren).
- You feel very tired and unwell. You have difficulties sleeping.
- You feel distressed and down. You feel afraid or anxious.

### Patient State 3

- You have a life-long incurable condition which sometimes causes swelling in different body parts. Swelling can be suddenly brought on by known or unknown triggers.
- You ***currently have*** swelling in your ***face (e.g. lips, cheeks, eyes)*** causing you discomfort or pain.

- Your general mobility and physical functioning are unaffected.
- Your speech or your eyesight may be affected by the swelling.
- You can wash and dress normally.
- You feel embarrassed about the appearance of your face, as you may get unwanted attention from other people in public spaces.
- You have some problems going about daily activities, such as work, housework, childcare and social activities. You do not feel comfortable leaving the house.
- You feel dependent on your partner/family for help.
- You feel very tired and unwell. You have difficulties sleeping.
- You feel distressed and down. You feel afraid or anxious that the swelling could spread to your throat, which would mean that you need to go to hospital immediately and that you may require emergency hospital admission for monitoring of your airways and breathing.

**Patient State 4**

- You have a life-long incurable condition which sometimes causes swelling in different body parts. Swelling can be suddenly brought on by known or unknown triggers.
- You ***currently have*** swelling in your ***hand*** causing you discomfort or pain.
- You are unable to use your hand normally which affects your physical functioning, specifically any task that requires use of your hand.
- It is difficult for you to wash and dress normally, so you rely on your partner/family for help.
- You do not want to leave your home because of your swelling. You feel embarrassed about the appearance of your hand.
- You have some problems going about daily activities, such as work, housework, childcare and social activities. You are unable to use your hand normally.
- You feel dependent on your partner/family for help around the house and childcare.
- You feel very tired and unwell. You have difficulties sleeping.
- You feel distressed and down. You feel anxious.

## Patient State 5

- You have a life-long incurable condition which sometimes causes swelling in different body parts. Swelling can be suddenly brought on by known or unknown triggers.
- You ***currently have*** swelling in your ***throat*** and ***face*** causing you considerable discomfort. You need to go to hospital immediately and may require emergency hospital admission for monitoring of your airways and breathing.
- You are currently resting. Your voice changes and your throat feels tight. You are experiencing difficulties swallowing and may find breathing more difficult.
- You cannot go about any normal daily activities, such as work, housework, childcare or social activities.
- You are completely dependent on your partner/family for help around the house and childcare.
- You feel very tired and unwell. You have difficulties sleeping because you are afraid to sleep.
- You feel very distressed and down, and very afraid and anxious because your breathing is affected and the risk of dying.

## Carer State

- A member of your family has a life-long incurable condition which sometimes causes swelling in different body parts. Swelling can be suddenly brought on by known or unknown triggers.
- They are currently experiencing swelling, and ***you are caring for them***.
- You help them to administer injections to treat their swelling. You also provide emotional support. You sometimes may need to assist them to wash or dress themselves. You might need to take them to hospital, if their swell is not controlled.
- Your normal daily activities, such as working, housework, childcare and social activities may be interrupted. You may need to take on more household tasks (e.g. cooking).
- You have adapted your lifestyle as a result of caring for someone with this condition.
- You feel distressed because your family member is unwell. You feel frustrated that the condition affects your family life. Administering treatment can be stressful for you.

## B19 - Interview script: TTO Valuation

### TIME TRADE-OFF INTERVIEW SCRIPT

Instructions for the interviewer are shown using **CAPITALISED TEXT**. These should **not** be read to the participant.

Instructions for the participant are shown using plain text. These should be read aloud to the participant.

#### POINTS TO MENTION WHEN STARTING AN INTERVIEW

Thank you for taking the time to participate in this study. The purpose of this study is to gain an understanding of the impact of a condition that causes swelling in different body parts, and to estimate the value that you would place on a treatment for their condition.

During the interview I will ask you to choose between different descriptions. These all describe the experiences of [an adult with this condition / caring for someone with this condition]. I will provide you with different patient and carer descriptions and ask you to think about how good or bad they are.

Before we begin, I would like to tell you a few things about the interview.

1. All the information you provide us will remain **confidential**. We only know your first name and, in our records, that name will be replaced with an ID number.

2. The interview will take **approximately 60 minutes** in total to complete. We will ask you to complete some forms as well as answer questions in the interview.

3. Please **take your time** answering the questions.

4. Please remember that there are **no right or wrong answers**. We are interested in your opinion and that is what is important to us. Do not worry about being consistent with previous answers and **feel free to change your mind** if you want to.

5. If you have **any questions throughout the interview**, please feel free to ask. We may have to wait until the end of the interview to answer some questions.

6. Your participation in this study is **voluntary**, so if at any time you would like to stop the interview please let me know.

7. Do you have **any questions** before we start?

**INTRODUCTION TO HEALTH STATES:**

The descriptions you are about to be shown relate to someone with a condition that causes swelling of different body parts.

---

**OVERVIEW:**

**START WITH THE FEELING THERMOMETER, THEN COMPLETE THE TTO EXERCISE. FOR EACH ONE, START WITH THE PRACTICE HEALTH STATES (AFTER FULL HEALTH AND DEAD).**

---

### Practice health states

We are going to go through two different tasks which we will use to get your views on these descriptions. We will explain these tasks with two practice descriptions. The purpose of this is to make sure you understand the tasks so please ask me if you have any questions as we go through.

---

### Feeling thermometer

The first method uses this scale.

**DISPLAY THERMOMETER**

---

We are going to use this scale to find out **how good or bad** you think each description is.

1. The scale runs from 0 to 100.

2. Down towards 0 are the very worst or the least preferred descriptions. The further down the scale that you place a description, the worse you believe it would be.

3. As you go up the scale the descriptions get better until you approach 100 where the very best descriptions could be located. The further up the scale you place a description, the better you believe it would be to experience.

4. I am going to ask you to read each description card and **then rate it on the scale to**

**indicate how good or bad you think it is.**

This is the first description that I would like you to read.

**REFER RESPONDENT TO "FULL HEALTH" CARD**

**LET RESPONDENT READ CARD**

---

This card describes full health.

Full health is equal to 100 on the scale and so we place it at 100. This is as good as your health can be.

This next card describes the state of being immediately dead.

---

**REFER RESPONDENT TO "DEAD" CARD**

**LET RESPONDENT READ CARD**

---

Looking at the scale, where would you place the dead card? Should you decide that you want to move this at any point, you are free to do so.

**REFER RESPONDENT THE INTRODUCTORY TEXT**

---

Please read this text and imagine you are the individual described. This text relates to all of the following descriptions which I am about to give you.

**START WITH PRACTICE HEALTH STATES (PRACTICE 1 AND PRACTICE 2)**

---

I will refer you the descriptions one at a time and I would like you to read each card carefully and think about **how good or bad it is**. Then I would like you to rate it on the scale. You may decide that a description is worse than dead and decide to place it lower down the scale.

When you read the cards imagine living as the person in the description for the **rest of your life.**

---

**REFER RESPONDENT TO CARD (PRESENT IN ORDER AS ASSIGNED FOR EACH PARTICIPANT)**

**WAIT FOR RESPONDENT TO COMPLETE RATING**

**GET NEXT CARD READY**

---

Now read this card and again **rate how good or bad** it is on the scale.

After you have rated a few cards you may wish to **move some of the ratings around on the scale**.

Please feel free to adjust the ratings if you need to.

---

**CONTINUE TO REFER TO CARDS ONE BY ONE TO RESPONDENT- MAKE SURE THEY RATE ALL HEALTH STATE CARDS**

BE AWARE THAT SOME PARTICIPANTS WILL INTERPRET THE SCALE THE WRONG WAY ROUND- PLACING THE WORST STATES TOWARDS 100. IF YOU SUSPECT THEY ARE DOING THIS THEN CHECK (**HAVE THEM CONFIRM THAT THEY BELIEVE THE STATES ARE CLOSER TO 'FULL HEALTH' OR 'DEAD' AS APPROPRIATE**).

IF THEY DON'T REALISE THEIR MISTAKE THEN CONTINUE TO THE END OF THE FEELING THERMOMETER TASK AND TERMINATE THE INTERVIEW. BE VERY WARY OF GUIDING PARTICIPANTS OR SUGGESTING TO THEM THAT THEIR ANSWERS ARE IN ANY WAY INCORRECT.

---

Now that you have rated all the cards on the scale, are there any changes you would like to make?

---

**PAUSE UNTIL RESPONDENT INDICATES SATISFACTORY COMPLETION OF ANY REVISIONS**

---

**IF THERE ARE ANY STATES RATED AS WORSE THAN DEAD THEN ASK PARTICIPANTS TO CONFIRM THAT THEY ARE WORSE THAN DEAD:**

---

- Now I would like to record your values for each card on the scale.
- Starting at the bottom of the scale, please refer to each card in turn and read off the value on the scale that you have given to that card.

- I will write down your answers.

Now we are ready to move onto the next stage in the interview.

Here we will ask you to rate the same description cards, but this time we will use a different method.

---

**REMOVE FEELING THERMOMETER**

---

## Health State Valuation Task

In this task we are going to use the same descriptions but using a different method.

In each question I will present you with a series of two choices and ask you to choose the one that you would prefer. If you think the **two choices are about the same tell me** and I will write this down. In order to make the task easier to understand we will use an aid similar to a game board.

**PLACE THE TTO BOARD NEXT TO YOU ON SCREEN.**

**SET SCALES TO BOTH SHOW ALIVE FOR 10 YEARS**

**PLACE FULL HEALTH STATE CARD ON LIFE A**

**REFER TO A HEALTH STATE CARD ON LIFE B**

The top part of the board is labelled Life A and the bottom part of the board is labelled Life B. These are two choices and we want to know which Life you would prefer. The cards describe the health status of each Life – or what each Life would be like the whole time.

**REFER TO THE LIFE A AND LIFE B CARDS**

The scale besides each card represents the period of time you can expect to live in this state for. For the purposes of this exercise please imagine that the longest that you can expect to live is 10 years.

Each scale will also show the number of years of life lost due to an early death.

**POINT TO SCALE A**

The pink colour on the scale shows the number years of Full Health.

**RUN FINGER ALONG PINK PART OF SCALE A**

You can expect to live 10 years, from today, after that you would die.

**POINT TO SCALE A**

The years of life lost due to an early death are shown by the black colour.

**MOVE THE SLIDER TO DEMONSTRATE A CHANGE IN DURATION.**

**POINT TO SCALE B**

The blue colour here in Life B represents the time you will live in Life B. Think about how good or bad Life B would be for you. In Life B you can expect to live a life as described on the card and you will live for 10 years, from today, followed by death.

Do you understand these ideas?

**YES- SET BOTH SCALES TO SHOW ALIVE FOR 10 YEARS AND CONTINUE BELOW**

**NO- REPEAT PREVIOUS PAGE.**

Please read the Full Health card again

**ALLOW RESPONDENT TIME TO READ FULL HEALTH CARD**

So the duration of Full Health is represented by the pink on the scale.

**START WITH THE TWO PRACTICE HEALTH STATES.**

---

**AFTER PRACTICE HEALTH STATES:**

**ASK PARTICIPANT IF THEY HAVE HAD ANY DIFFICULTY WITH THE PRACTICE TASK AND IF NOT IF THEY ARE HAPPY TO MOVE ON TO THE MAIN TASK.**

**IF THEY CONFIRM THEIR UNDERSTANDING AND YOU FEEL THEY HAVE UNDERSTOOD, RETURN TO TTO BOARD AND GO THROUGH THE STUDY HEALTH STATES.**

**IF PARTICIPANT IS UNSURE, OR IF YOU ARE NOT SURE THEY UNDERSTAND, EXPLAIN THE TASK AGAIN AND REPEAT THE PRACTICE EXERCISE, CONFIRMING THEIR UNDERSTANDING THROUGHOUT.**

---

**IF AFTER REPEATING THE PRACTICE EXERCISE, THE PARTICIPANT DOES NOT UNDERSTAND OR IS NOT ENGAGED IN THE EXERCISE, TERMINATE THE INTERVIEW.**

---

**FOR FIRST HEALTH STATE PLEASE READ OUT ADDITIONAL TEXT IN ITALLICS BELOW, FOR OTHER HEALTH STATES SET SCALE A TO 10 YEARS, REFER TO THE NEXT HEALTH STATE CARD AND READ TEXT NOT IN ITALICS**

This is the first description. Please read this card carefully.

Life B is represented by this description.

Let's start the first question by working through it together. The top part of the board represents Life A. The card describes Full Health. The duration of Life A is shown by the pink part of the scale.

***POINT TO LIFE A***

The scale shows that Full Health will last for 10 years followed by death.

The bottom card and time scale describe Life B. This is the description that you have just read. The bottom time scale, marked in blue, shows that this state will last for 10 years followed by death.

***POINT TO THE SLIDER ON LIFE A SHOWING THE DURATION***

1. Which Life would you prefer, 10 years in Life A or 10 years in Life B, or are they about the same?

***IF PARTICIPANT IS UNSURE AT ANY STAGE:***

Would you like me to explain this again?

**A- MOVE LIFE A SCALE TO 0 YEARS (ALL BLACK) AND CONTINUE**

**B - ASK "WHY?" MARK RESPONSE (Prefer B: 1.0, and note reason given)**

**SAME - MARK RESPONSE (Equal: 1.00)**

---

2. Now I've changed the Life A time scale to 0 which can be considered as 'dead'. Which Life would you prefer now? 10 years in Life B or being 'dead'?

## A or SAME – <u>GO TO LT-TTO INTERVIEW GUIDE (page 11)</u>

**B - MOVE SCALE A TO 9.5 YEARS AND CONTINUE**

---

3. Now Life A represents 9 years and 6 months of Full Health in total. Which Life would you prefer now? Or are they about the same?

**A – MOVE SCALE A TO 0.5 YEARS,**

**B - MARK RESPONSE (Prefer B: 0.975) GO TO THE NEXT HEALTH STATE**

**SAME - MARK RESPONSE (Equal: 0.950)**

---

4. Now you have 6 months of Full Health followed by death in Life A. Which Life would you prefer? Or are they about the same?

**A – MARK RESPONSE (Prefer A: 0.025), GO TO THE NEXT HEALTH STATE.**

**B - MOVE SCALE A TO 9 YEARS AND CONTINUE**

**SAME - MARK RESPONSE (Equal: 0.050)**

---

5. Now you have 9 years of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

**A – MOVE SCALE A TO 1 YEARS AND CONTINUE**

**B - MARK RESPONSE (Prefer B: 0.925) GO TO THE NEXT HEALTH STATE**

**SAME – MARK RESPONSE (Equal: 0.900)**

---

6. Now you have 1 year of Full Health followed by death in Life A which Life would you prefer? Or are they about the same?

**A - MARK RESPONSE (Prefer A: 0.075), GO TO THE NEXT HEALTH STATE.**

**B - MOVE SCALE A TO 8.5 YEARS AND CONTINUE**

**SAME - MARK RESPONSE (Equal: 0.100)**

---

7. Now you have 8 years and 6 months of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

**A – MOVE SCALE A TO 1.5 YEARS AND CONTINUE**

**B- MARK RESPONSE (Prefer B: 0.875) GO TO THE NEXT HEALTH STATE**

**SAME - MARK RESPONSE (Equal: 0.850)**

---

8. Now you have 1 year and 6 months of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

**A - MARK RESPONSE (Prefer A: 0.125), GO TO THE NEXT HEALTH STATE.**

**B - MOVE SCALE A TO 8 YEARS AND CONTINUE**

**SAME – MARK RESPONSE (Equal: 0.150)**

---

9. Now you have 8 years of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

**A – MOVE SCALE A TO 2 YEARS,**

**B - MARK RESPONSE (Prefer B: 0.825) GO TO THE NEXT HEALTH STATE**

**SAME – MARK RESPONSE (Equal: 0.800)**

---

10. Now you have 2 of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

**A - MARK RESPONSE (Prefer A: 0.175), GO TO THE NEXT HEALTH STATE.**

**B - MOVE SCALE A TO 7.5 YEARS AND CONTINUE**

**SAME – MARK RESPONSE (Equal: 0.200)**

---

11. Now you have 7 years and 6 months of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

**A – MOVE SCALE A TO 2.5 YEARS,**

**B - MARK RESPONSE (Prefer B: 0.775) GO TO THE NEXT HEALTH STATE**

**IF HEALTH STATES SAME – MARK RESPONSE (Equal: 0.750)**

---

12. Now you have 2 years and 6 months of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

**A – MARK RESPONSE (Prefer A: 0.225), GO TO THE NEXT HEALTH STATE.**

**B - MOVE SCALE A TO 7 YEARS AND CONTINUE**

**SAME – MARK RESPONSE (Equal: 0.250)**

---

13. Now you have 7 years of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

**A – MOVE SCALE A TO 3 YEARS**

**B - MARK RESPONSE (Prefer B: 0.725) GO TO THE NEXT HEALTH STATE**

**SAME – MARK RESPONSE (Equal: 0.700)**

---

14. Now you have 3 years of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

**A - MARK RESPONSE (Prefer A: 0.275), GO TO THE NEXT HEALTH STATE.**

**B - MOVE SCALE A TO 6.5 YEARS AND CONTINUE**

**SAME – MARK RESPONSE (Equal: 0.300)**

---

15. Now you have 6 years and 6 months of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

**A – MOVE SCALE A TO 3.5 YEARS AND CONTINUE**

**B- MARK RESPONSE (Prefer B: 0.675) GO TO THE NEXT HEALTH STATE**

**SAME – MARK RESPONSE (Equal: 0.650)**

---

16. Now you have 3 years and 6 months of Full Health followed by death in Life A , which Life would you prefer? Or are they about the same?

**A - MARK RESPONSE (Prefer A: 0.325), GO TO THE NEXT HEALTH STATE.**

**B - MOVE SCALE A TO 6 YEARS AND CONTINUE**

**SAME – MARK RESPONSE (Equal: 0.350)**

---

17. Now you have 6 years of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

**A – MOVE SCALE A TO 4 YEARS,**

**B - MARK RESPONSE (Prefer B: 0.625) GO TO THE NEXT HEALTH STATE**

**SAME – MARK RESPONSE (Equal: 0.600)**

---

18. Now you have 4 years of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

**A - MARK RESPONSE (Prefer A: 0.375), GO TO THE NEXT HEALTH STATE.**

**B - MOVE SCALE A TO 5.5 YEARS AND CONTINUE**

**SAME – MARK RESPONSE (Equal: 0.400)**

---

19. Now you have 5 years and 6 months of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

**A – MOVE SCALE A TO 4.5 YEARS,**

**B - MARK RESPONSE (Prefer B: 0.575) GO TO THE NEXT HEALTH STATE**

**SAME – MARK RESPONSE (Equal: 0.550)**

---

20. Now you have 4 years and 6 months of Full Health followed by death in Life A, which Life would you prefer? Or are they about the same?

**A - MARK RESPONSE (Prefer A: 0.425), GO TO THE NEXT HEALTH STATE.**

**B - MOVE SCALE A TO 5 YEARS AND CONTINUE**

**SAME – MARK RESPONSE (Equal: 0.450)**

---

21. Now you have 5 years of Full Health followed by death in Life A, which Life would you prefer?

Or are they about the same?

**A - MARK RESPONSE (Prefer A: 0.475) GO TO THE NEXT HEALTH STATE**

**B – MARK RESPONSE (Prefer B: 0.525), GO TO THE NEXT HEALTH STATE.**

**SAME - MARK RESPONSE (Equal: 0.500)**

---

# LEAD-TIME TTO INTERVIEW GUIDE

Given that this is how you feel about this description I am going to ask you a bit more about it using a slightly different method

**SHOW THE LT-TTO BOARD (OTHER SIDE OF BOARD).**

**SET LIFE A TO SHOW ALIVE FOR 10 YEARS**

**REFER TO FULL HEALTH STATE CARD ON PLACEHOLDER TO THE LEFT**

**REFER TO HEALTH STATE CARD ON PLACEHOLDER TO THE BOTTOM RIGHT**

On the board you can see two scales both showing 20 years. The top scale is labelled Life A and the bottom scale is labelled Life B. As before, we want to know which you prefer, imagining that you are the individual described.

Please imagine that in the top scale, Life A, you would live for 10 years, from today, in the pink Full Health state described on the left, and then you would die. In the bottom scale, Life B, you would live for 10 years, from today, in the pink Full Health state described on the left, followed by 10 years as the person described on the bottom, and then you would die.

Do you understand these ideas?

**WITH THE MARKER FOR LIFE A SET TO 10 YEARS**

3. Now, do you prefer Life A, Life B, or are they about the same?

**A – MOVE SCALE A TO 0 YEARS AND CONTINUE.**

**B - MARK RESPONSE (Prefer B: 0.0) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**SAME – MARK RESPONSE (Equal: 0.0)**

---

4. Now I've changed Life A to 0 which can be considered as 'dead'. Which Life do you prefer now or are they about the same?.

**A – MARK RESPONSE (Prefer A: -1.0) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**B- MOVE SCALE A TO 9.5 YEARS AND CONTINUE.**

**SAME – MARK RESPONSE (Equal: -1.000)**

---

5. Now you have 9 years and 6 months of Full Health followed by death in Life A, which Life would you prefer or are they about the same?

**A - MOVE SCALE A TO 0.5 YEARS AND CONTINUE.**

**B - MARK RESPONSE (Prefer B: -0.025) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**SAME – MARK RESPONSE (Equal: -0.050)**

---

6. Now you have 6 months of Full Health followed by death in Life A, which Life would do you prefer or are they about the same?

**A – MARK RESPONSE (Prefer A: -0.975) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**B-MOVE SCALE A TO 9 YEARS AND CONTINUE.**

**SAME – MARK RESPONSE (Equal: -0.950)**

---

7. Now you have 9 years of Full Health followed by death in Life A, which Life would you prefer or are they about the same?

**A - MOVE SCALE A TO 1 YEAR AND CONTINUE.**

**B - MARK RESPONSE (Prefer B: -0.075) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**SAME – MARK RESPONSE (Equal: -0.100)**

---

8. Now you have 1 year of Full Health followed by death in Life A, which Life do you prefer or are they about the same?

**A – MARK RESPONSE (Prefer A: -0.925) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**B-MOVE SCALE A TO 8.5 YEARS AND CONTINUE.**

**SAME – MARK RESPONSE (Equal: -0.900)**

---

9. Now you have 8 years and 6 months of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

**A - MOVE SCALE A TO 1.5 YEARS AND CONTINUE.**

**B - MARK RESPONSE (Prefer B: -0.125) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**SAME LIFE – MARK RESPONSE (Equal: -0.150)**

---

10. Now you have 1 year and 6 months of Full Health followed by death in Life A, which Life do you prefer, or are they about the same?

**A – MARK RESPONSE (Prefer A: -0.875) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**B-MOVE SCALE A TO 8 YEARS AND CONTINUE.**

**SAME – MARK RESPONSE (Equal: -0.850)**

---

11. Now you have 8 years of Full Health followed by death in Life A, which Life would you prefer or are they about the same?

**A - MOVE SCALE A TO 2 YEARS AND CONTINUE.**

**B - MARK RESPONSE (Prefer B: -0.175) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**SAME – MARK RESPONSE (Equal: -0.200)**

---

12. Now you have 2 years of Full Health followed by death in Life A, which Life would you prefer or are they about the same?

**A – MARK RESPONSE (Prefer A: -0.825) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**B-MOVE SCALE A TO 7.5 YEARS AND CONTINUE.**

**SAME – MARK RESPONSE (Equal: -0.800)**

---

13. Now you have 7 years and 6 months of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

**A - MOVE SCALE A TO 2.5 YEARS AND CONTINUE.**

**B - MARK RESPONSE (Prefer B: -0.225) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**IF HEALTH STATES SAME – MARK RESPONSE (Equal: -0.250)**

---

14. Now you have 2 years and 6 months of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

**A – MARK RESPONSE (Prefer A: -0.775) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**B-MOVE SCALE A TO 7 YEARS AND CONTINUE.**

**SAME – MARK RESPONSE (Equal: -0.750)**

---

15. Now you have 7 years of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

**A - MOVE SCALE A TO 3 YEARS AND CONTINUE.**

**B - MARK RESPONSE (Prefer B: -0.275) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**SAME- MARK RESPONSE (Equal: -0.300)**

---

16. Now you have 3 years of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

**A – MARK RESPONSE (Prefer A: -0.725) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**B-MOVE SCALE A TO 6.5 YEARS AND CONTINUE.**

**SAME – MARK RESPONSE (Equal: -0.700)**

---

17. Now you have 6 years and 6 months of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

**A - MOVE SCALE A TO 3.5 YEARS AND CONTINUE.**

**B - MARK RESPONSE (Prefer B: -0.325) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**SAME – MARK RESPONSE (Equal: -0.350)**

---

18. Now imagine you have 3 years and 6 months of Full Health followed by death in Life A, which Life would you prefer or are they about the same?

**A – MARK RESPONSE (Prefer A: -0.675) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**B-MOVE SCALE A TO 6 YEARS AND CONTINUE.**

**IF HEALTH STATES SAME – MARK RESPONSE (Equal: -0.650)**

---

19. Now you have 6 years of Full Health followed by death in Life A, which Life would you prefer or are they about the same?

**A - MOVE SCALE A TO 4 YEARS AND CONTINUE.**

**B - MARK RESPONSE (Prefer B: -0.375) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**SAME – MARK RESPONSE (Equal: -0.400)**

---

20. Now you have 4 years of Full Health followed by death in Life A, which Life would you prefer or are they about the same?

**A – MARK RESPONSE (Prefer A: -0.625) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**B-MOVE SCALE A TO 5.5 YEARS AND CONTINUE.**

**SAME – MARK RESPONSE (Equal: -0.600)**

---

21. Now you have 5 years and 6 months of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

**A - MOVE SCALE A TO 4.5 YEARS AND CONTINUE.**

**B - MARK RESPONSE (Prefer B: -0.425) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**SAME – MARK RESPONSE (Equal: -0.450)**

---

22. Now you have 4 years and 6 months of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

**A – MARK RESPONSE (Prefer A: -0.575) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**B-MOVE SCALE A TO 5 YEARS AND CONTINUE.**

**SAME – MARK RESPONSE (Equal: -0.550)**

---

23. Now you have 5 years of Full Health followed by death in Life A, which Life would you prefer, or are they about the same?

**A - MARK RESPONSE (Prefer A: -0.525) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**B – MARK RESPONSE (Prefer B: -0.475), GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

**IF HEALTH STATES SAME - MARK RESPONSE (Equal: -0.500) GO TO THE NEXT HEALTH STATE (TTO PROCEDURE, PAGE 4)**

---

**<u>AT THE END OF THE INTERVIEW</u>, ASK THE FOLLOWING QUESTIONS ABOUT ANY HEALTH STATES VALUED AS WORSE THAN DEAD (LT-TTO PROCEDURE)**

- Are you aware that answer you gave for this description suggests that being the person in this description is worse than being dead?
- Knowing this now, would you change how you evaluated this description?

**NOTE RESPONSES IN THE NOTES COLUMN ON THE SCORE SHEET FOR**

**THE RELEVANT HEALTH STATE.**

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# Single technology appraisal

# Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

# Clarification questions

**January 2021**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| **ID1624 Berotralstat ERG Clarification letter to company - 2nd response v1.0 [ACIC]** | **V1.0** | **Yes** | **18.02.2021** |

**B22. PRIORITY.** Given the very small numbers of patients in the subgroups used to inform the economic model, and a lack of evidence to support previous experience of androgens or baseline attack frequency as effect modifiers, please provide a scenario analysis 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). Please also provide scenario analyses that combine these changes with those requested in questions B4, B8 (d).

The clinical parameters used to inform the population of patients with ≥2 attacks at baseline are presented in Table 1.

**Table 1: Clinical parameters used to inform the ≥2 attacks at baseline population**

| 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] |

Following review of the implementation of the scenarios presented in Table 2 (Table 26 of the original response) it was identified that the title “B22 & B4 (≥2 attacks per month; berotralstat mean attack rate, SoC baseline attack rate applied thoughout)” should be titled “B22 & B4 (≥2 attacks per month; berotralstat mean attack rate, SoC mean attack rate”, as this is more accurately what this scenario represents. This has been corrected in Table 2.

The results for the updated scenario “B22 & B4 (≥2 attacks per month; berotralstat mean attack rate, SoC baseline attack rate applied thoughout)” have been added into Table 2.

**Table 2: B22 Scenario analyses – incremental cost-effectiveness results**

| | Berotralstat | SoC |
|---|---|---|
| **B22 (≥2 attacks per month)** | | |
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |
| **Alternative B22 (≥2 attacks per month, SoC baseline attack rate applied thoughout)** | | |
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |
| **B22 & B4 (≥2 attacks per month; berotralstat mean attack rate, SoC baseline attack rate applied thoughout)** | | |
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |
| **B22 & B4 (≥2 attacks per month; berotralstat mean attack rate, SoC mean attack rate)** | | |
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |

| | | |
|---|---|---|
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |
| **B22 & B8d (≥2 attacks per month; responder baseline attack rate applied)** | | |
| Total costs (£) | [redacted] | [redacted] |
| Total LYG | [redacted] | [redacted] |
| Total QALYs | [redacted] | [redacted] |
| Incremental costs (£) | [redacted] | [redacted] |
| Incremental LYG | [redacted] | [redacted] |
| Incremental QALYs | [redacted] | [redacted] |
| ICER versus baseline (£/QALY) | [redacted] | [redacted] |
| ICER incremental (£/QALY) | [redacted] | [redacted] |

## Updated Scenario Analyses results

A version of the cost-effectiveness model (CEM) with all scenarios implemented has been provided alongside this response. As the scenarios were implemented in separate versions of the CEM, this required combining all scenarios into a single model. Scenario analysis results using the combined CEM are presented in

Table 3. There are two differences compared with the results presented in the original response:

- The two B4 scenarios have been updated, as the previous CEM versions used hard-coded values for certain parameters, which have now been calculated in the combined CEM. The differences in the ICERs are extremely minor (less than £200 in both cases) and should not impact decision-making.
- In the original response, the scenario titled “B17 (Acute costs -10%)” erroneously presented the net monetary benefit as opposed to the ICER. This result has also been updated in

- Table **3**.

**Table 3: Summary of ERG requested scenarios updated**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| **B4 (SoC baseline attack rate applied throughout)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B4 (average attack rates applied)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B5 (pooled attack rate)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B8d (responder baseline attack rate and reductions applied)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B11 (caregiver disutility excluded)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B13 (attack-free EQ-5D)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B15 (individual berinert administration applied)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **B16 (actual standard errors) – Probabilistic results** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **B17 (Acute costs +10%)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **B17 (Acute costs -10%)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **B18 (Treatment waning: 5 years)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **B18 (Treatment waning: 10 years)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **B18 (Treatment waning: 20 years)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **B22 (≥2 attacks per month)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **Alternative B22 (≥2 attacks per month, SoC baseline attack rate applied thoughout)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |
| **B22 & B4 (≥2 attacks per month; berotralstat mean attack rate, SoC baseline attack rate applied thoughout)** | | | | | | | | |
| SoC | [redacted] | | | | | | | |
| Berotralstat | [redacted] | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **B22 & B4 (≥2 attacks per month; berotralstat mean attack rate, SoC mean attack rate)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **B22 & B8d (≥2 attacks per month; responder baseline attack rate applied)** | | | | | | | | |
| SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

NICE National Institute for Health and Care Excellence

## Patient organisation submission

# Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

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

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

**Information on completing this submission**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

| **About you** | |
|---|---|
| 1.Your name | [redacted] |

| | |
|---|---|
| 2. Name of organisation | HAE UK |
| 3. Job title or position | [redacted] |
| 4a. Brief description of the organisation (including who funds it). How many members does it have? | HAE UK (registered charity 1152591) is a support and advocacy organisation for people and families affected by Hereditary Angioedema. We have circa 650 people registered with us who either have a diagnosis of hereditary angioedema or are relatives/carers for such a person. We also provide support and advice to people affected by Acquired Angioedema (acquired C1-INH deficiency).<br><br>Amongst our activities are; Educational Patient days (2020 provided virtually!) with expert clinicians providing information about the condition, treatments and research projects. Patient and clinician information and training with projects such as our Nurse Training Programme and 'Expert Patient' resources. We campaign and lobby both as individual organisation and as part of Genetic Alliance, Rare Disease UK and The Specialised Health Care Alliance for increased awareness and improved access to treatments. We attend clinic, departmental and workplace/school meetings to raising awareness of Hereditary Angioedema amongst the general populace and with clinicians.<br><br>HAE UK also provides sponsorship of research into management of Hereditary Angioedema, particularly the psychological effects of living with long term, potentially fatal conditions. We are also assisting in a project investigating non-pharmaceutical methods of reducing and/or controlling attacks by improving fitness levels.<br><br>HAE UK is funded by donations from members, payroll donation, fundraising activities such as half-marathon runners, family fun days etc. We are also in receipt of unrestricted grants from pharma companies CSLBehring, Takeda, Pharming, Kalvista and Biocryst which we use to support our activities such as the educational Patient Days. |
| 4b. Has the organisation received any funding from the manufacturer(s) of the | Biocryst; £3000 December 2019 for redevelopment and reprinting of patient literature<br>£2000 October/November 2020 for inviting participants and moderating 2 x Patient Advisory Board meetings |

| | |
|---|---|
| technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]<br><br>If so, please state the name of manufacturer, amount, and purpose of funding. | CSL Behring £35,000 April 2020 unrestricted grant for provision of patient support activities including 24hr telephone helpline<br><br>Takeda £3020 March 2020 for Virtual Conferencing provision to enable communication with members during 'lockdown' |
| 4c. Do you have any direct or indirect links with, or funding from, the tobacco industry? | NO |
| 5. How did you gather information about the experiences of patients and carers to include in your submission? | Day to day contact with patients (telephone, electronic), on-line Patient Questionnaires, Opinions and experiences discussed during patient advisory board meetings, virtual Patient Day meeting, virtual meetings during 'lockdown'<br>Real quotes from patients have been put in inverted commas in the following submission and highlighted in blue. |

| Living with the condition | |
|---|---|
| 6. What is it like to live with the condition? What do carers experience when caring for someone with the condition? | Hereditary Angioedema is characterised by unpredictable and sporadic attacks of subcutaneous swelling which can attack anywhere and varies from mild to lifethreatening if it affects airways. Historically, it is considered that over 30% of people affected by HAE died from airway obstruction. It is still a major concern to patients, as many of them have lost a family member this way in the past.<br><br>Attacks can occur in feet, hands and limbs, abdominally, genitally, facially and elsewhere. Swellings reach a very large size in a short time - circa 30-40 minutes - and then take 2 or more days to resolve if left untreated. Available treatments will stop swelling progressing, but will not help it to resolve. HAE swelllings are unresponsive to antihistamines or steroids. It is not unusual for swellings to occur in more than one location in an attack. There are no particular triggers for these attacks, as in allergic conditions, but some common triggers emerge, notably hormonal changes, stress and anxiety (eg exams or even 'happy stress ' like family events) invasive procedures such as dentistry, minor surgery, infections such as colds, flue, tooth decay. Sometimes repetitive actions such as painting, even walking can trigger attacks.<br><br>These swellings can make normal daily activities impossible, with swollen feet unable to wear shoes, swollen hands preventing use of cutlery, writing equipment, tablets etc. Abdominal swellings can mean patients have to wear very loose clothing and they are often in extreme pain.<br><br>A large number of patients are well managed with oral attenuated androgens, however many people find unacceptable side effects such as androgenisation, weight gain, temperament changes and of course they cannot be used with women considering pregnancy. Attenuated androgens are no longer manufactured in UK and have become increasingly difficult to source, meaning more patients are no turning to ad hoc use of acute treatments. These are intravenous C1-Esterase Inhibitor and Icatibant, which is administered subcutaneously<br><br>A cohort of patients suffer such frequent attacks (more than two a week) that they are allowed to use C1-INH as prophylaxis, and others fulfilling the same criteria are now prescribed subcutaneous Lanadelumab.<br><br>Patients express the uncertainty of living with HAE and exhibit heightened levels of anxiety, never knowing when an attack might happen 'I go to bed every night and at the back of my mind is the thought I might wake up with a swelling – or not wake up' |

| | |
|---|---|
| | This uncertainty leads them to be uncertain about making arrangements for work, educational or social arrangements. ‘we used to plan family parties or get-togethers and yet never be able to get there’ People often describe how they missed events such as family weddings because an attack had occurred, and similarly they have had excessive amounts of time off school and missed crucial exam dates. ‘My daughter has had to live with the fact that she cannot go on school trips because I may not be able to get there to give her treatment’ and, shockingly, from a parent with HAE who was only diagnosed after her daughter was diagnosed at an early age, ‘my daughter used to get teased at school because of the swellings, and they would lie in wait for her and punch her to make her swell. We changed her school, but I can’t forgive myself for having given her this condition’ The guilt of having ‘passed on’ this condition is often described by parents, who often also are worried that a child will not inform them of a swelling soon enough for them to administer any treatment. This is usually because they have a memory of a parent or grandparent dying, 'Mum was very sick all of her life and passed away in 1969 at the age of 24. Her death was caused by a swelling in her throat, unfortunately medical attention came too late.'<br><br>Another member says ‘Having this disease has taken my life; my education, my prospect of a career, having a family’<br><br>Conversely, a happier note from another, ‘starting with preventative treatment at 15 got me through school and uni to a good degree’ |

| Current treatment of the condition in the NHS | |
|---|---|
| 7. What do patients or carers think of current treatments and care available on the NHS? | There has been a considerable improvement in the availability of modern treatments particularly since the two NHS England documents on treatment of acute attacks and the later (2016) use of C1-inhibitor (C1-INH) as prophylaxis<br><br>ACUTE/ON-DEMAND TREATMENTS;<br><br>Icatibant, prefilled syringe; subcutaneous injection best administered as soon in an attack as possible. Blocks bradykinin receptors, but short half life means treatment often has to be repeated. Easy for patients to administer and keep at home. The product is now licenced for paediatric use, but it can be quite a painful injection with considerable irritation at the injection site. Patient responses vary 'Icatibant is brilliant! I wish it had been around when I was at my worst in my 30s and 40s' 'I was 80 when I gave myself my first injection!' but some find it less effective; 'When it works it is great, but I often have to give myself a second one, then a third and then I have to go to A&E for C1' '(Daughter) won't use it because her dad uses it and he says it is really painful'<br><br>C1-INH; there are three licensed products, two plasma derived and one recombinant, all licensed for paediatric and adult use. These are infused intravenously, although there is a subcutaneous preparation (not widely available in UK , only on IFR) used prophylactically. This is effectively a replacement product and the advantage of the recombinant is the avoidance of possible viral transmission which is still a possibility with plasma products. Many patients use this ad hoc but some are unable to self cannulate and so attend A&E or have an 'infusion buddy' usually a relative. Having C1-INH at home has reduced a great deal of the anxiety that patients feel about their condition, however it is a reasonably lengthy process to reconstitute, infuse and then patients are recommended to rest for 30 minutes. 'It sounds awful, but when my partner gets the needle into the vein I know it's all going to be alright' 'Fortunately I had my own supply of C1-INH with me. I always carry it with me when I go to work in case of an attack when I am too far from home and that has now proved to be the right thing to do! |

| | |
|---|---|
| | Despite having the C1-INH and a letter from my immunologist, there was still a bit of fuss about giving me the injections, but taking my own supply definitely sped things up and after about half an hour the C1-INH was being administered.'<br>'Being allowed to keep C1 at home was life-changing. I was able to plan and went on holiday with my family for the first time.'<br><br>PROPHYLAXIS TREATMENTS-ORAL<br><br>Attenuated Androgens; Oral tablets. Stimulate the liver to produce more C1-INH; can be effective prophylaxis for patients but most still have breakthough attacks that require more treatment usually intravenous C1-INH. Some patients suffer extreme side-effects eg masculinisation, weight gain, mood swings. All patients must have regular liver monitoring, and as described above this product is no longer manufactured in UK. It is having to be sourced from abroad and is believed to be considerably more expensive than previously. These are the only HAE treatment that is provided under 'Shared Care' arrangements. 'I have had to come off danazol as I developed liver cancer and now am having to learn how give myself C1' 'been on it for years and no problems but now my doctor says he can't prescribe it'.<br><br>Tranexamic Acid; Tablets or liquid, seems most effective for patients affected by a mutation in the FXII gene. It inhibits plasminogen and so reduces bradykinin production. Only about 1/10 patients find it effective, but those who do, do not report side-effects. Again, breakthrough attacks may require Icatibant or IV C1-INH. It is licensed for use as prophylaxis in children, but many GPs will not prescribe the liquid form as it is more expensive.<br><br>PROPHYLAXIS TREATMENT-INJECTABLE<br><br>C1-INH prophylaxis – under guidance from the NHS England Commissioning document 2016 patients having two or more attacks per week can be maintained on twice weekly C1-INH infusions. Some patients still have break through attacks, as the half life varies from patient to patient but can be as little as 36 hours for some patients. |

| | |
|---|---|
| | Lanadelumab – sub cutaneous injection kallikrein inhibitor. Recently approved and still under 'black triangle'. Same criteria as C1-INH. Initiated at once per fortnight, then once stable reduced to once per month. 'got my life back!' 'my daughter has gone from swelling three times a week to breakthrough swelling once a month. Her mood is much better as she's not anxious all the time…' |
| 8. Is there an unmet need for patients with this condition? | As can be seen from the descriptions above, the most effective treatments for this debilitating condition are injectable products. The existing oral products are only effective in the least badly effective patients and still requires i/v C1-iNH 'rescue'. There are also concerns over supply and increase in price due to unavailability. This is driving more patients to use ad-hoc C1-INH or Icatibant. A significant number of C1-INH users attend A&E in order to be infused as they cannot self cannulate. Many also find Icatibant unpleasant to use and so defer injecting it until the attack is too advanced for it to really be effective.<br><br>Many of the frequent C1-INH users have poor veins due to the frequent cannulation , 'I am fed up with thinking it's infusion day my veins are disappearing and as much as I don't mind doing Infusions it is still stressful . My husband does it with me and I'm always relieved when it's done without blowing up or hurting'.<br><br>The patient ad-board also pointed out the difficulty of the routine, being every so often rather than regularly; also travelling with syringes etc which causes issues with airlines, customs etc. Storage of large quantities of infusion disposables etc and lanadelumab has to be refrigerated and brought to room temperature before injecting. |
| **Advantages of the technology** | |
| 9. What do patients or carers think are the advantages of the technology? | The advance of an effective oral product is regarded as the 'Grail' by many patients. The simplicity of single, daily tablet dosing is convenient and unobtrusive, as many people are embarrassed by having to carry syringes etc around with them when travelling or staying away. There is also no issue with disposables. |

| | |
|---|---|
| | Young adults are more easily persuaded to take a tablet than to give themselves an infusion. No need for special training or nurse time to train patients. There are no concerns about supply or fluctuations in the market as there are with plasma derived products, Oral products will be of benefit for patients who are needle phobic. |
| **Disadvantages of the technology** | |
| 10. What do patients or carers think are the disadvantages of the technology? | Many of the older patients tend to think that only the injectables can be effective, and parents/carers are often comforted by the fact that they have physically 'treated' their charge.<br>From one patient who was on the clinical trial I heard 'I got very anxious waiting to have an attack because I was going for so long with not having one and I couldn't believe it' |
| **Patient population** | |
| 11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why. | There is a large cohort of patients who have frequent attacks but fall outside of the criteria for injectable prophylaxis. They are reliant on ad hoc treatment rather than being able to have a simple form of prophylaxis which will make them able to lead a 'normal' life. To be able to prevent attacks allows people to lead a 'normal' life, attending education and having jobs and contribute to society.<br>It is possible that because of inhibiting kallikrein this product will be of benefit to the patients with HAE with normal C1, who currently have no reliable form of treatment although some may respond to tranexamic acid.<br>Some of the very unstable HAE patients may not find this product as effective for them as they have too many severe attacks. |

| | |
|---|---|
| **Equality** | |
| 12. Are there any potential equality issues that should be taken into account when considering this condition and the technology? | This product should be available without restriction to all Immunology centres for them to prescribe to suitable patients. |
| **Other issues** | |
| 13. Are there any other issues that you would like the committee to consider? | Hereditary Angioedema presents in many different ways and it is not unusual to find families with several diagnosed close family members expressing the condition in very different ways. For example, a pair of (non-identical) twins where one sister is severely affected and the other has not to date had an attack.<br>Consequently, it is our opinion that there should be as wide a choice of medication available to patients and clinicians as possible. It must be recognised that a patient whilst requiring life time treatment may not require the same product or regimen at all stages of their life. Treatment should be able to be varied according to agreement between clinician and patients. This is is more cost effective to the NHS as appropriate treatment may be targeted to the patient. This technology which is shown to be effective, with few side-effects and providing control of symptoms and with the easy administration of once a day tablet is a very useful addition to the products clinicians can use to manage this debilitating condition. |

| **Key messages** |
| --- |
| 14. In up to 5 bullet points, please summarise the key messages of your submission:<br><br>• This is a new product that has been shown to provide effective control of HAE symptoms with an easy once daily oral presentation.<br>• Many patients who do not qualify for injectable prophylaxis will benefit from this product as older, less effective products become unavailable.<br>• Increased choice for clinicians and patients<br>• No need for training by specialist nurses in administration<br>• Will reduce need for use of injectables for ad hoc administration |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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NICE National Institute for Health and Care Excellence

## Professional organisation submission

# Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

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

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

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

**Information on completing this submission**

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- Your response should not be longer than 13 pages.

| **About you** | |
|---|---|
| 1. Your name | [redacted] |
| 2. Name of organisation | **British Society for Allergy and Clinical Immunology** |

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|---|---|
| 3. Job title or position | [redacted] |
| 4. Are you (please tick all that apply): | ☐ an employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ a specialist in the treatment of people with this condition?<br>☐ a specialist in the clinical evidence base for this condition or technology?<br>☐ other (please specify): |
| 5a. Brief description of the organisation (including who funds it). | **BSACI is a registered charity for the improvement of allergy through education and research** |
| 4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] | **No** |

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| If so, please state the name of manufacturer, amount, and purpose of funding. | |
| 5c. Do you have any direct or indirect links with, or funding from, the tobacco industry? | **No** |
| **The aim of treatment for this condition** | |
| 6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.) | To reduce the frequency and severity of angioedema episodes in patients with angioedema related to hereditary angioedema (HAE) / C1 inhibitor deficiency. The aim is to prevent attacks of swelling / angioedema by blocking the metabolic pathway that leads to increases in bradykinin (the main mediator of swelling in HAE). |
| 7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by | Reduction in swelling frequency of around / greater than 50% when used prophylactically. However, a reduction in both severity and frequency would constitute a significant benefit to patients, particularly if achievable with a well-tolerated oral medication |

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| x cm, or a reduction in disease activity by a certain amount.) | |
| 8. In your view, is there an unmet need for patients and healthcare professionals in this condition? | Definitely – current treatment options and commissioning criteria make it very difficult to offer patients beneficial treatments; effective treatments exist but are severely limited to the patients most extremely affected. This leaves a large cohort of patients with moderate to severe (but not extremely severe disease) that do not have access to effective well-tolerated therapy. In addition, patients with difficult intravenous access and needle phobia and, children and adolescents in need of prophylaxis who are unable to take attenuated androgens would benefit from this medication. |
| **What is the expected place of the technology in current practice?** | |
| 9. How is the condition currently treated in the NHS? | Specialist care (immunology and allergy); part of specialised services as a rare disease |
| • Are any clinical guidelines used in the treatment of the condition, and if so, which? | There are a series of national and international consensus / guideline documents. Including:<br>https://waojournal.biomedcentral.com/articles/10.1186/s40413-017-0180-1<br>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4449776/<br>Commissioning criteria also exist: https://www.england.nhs.uk/wp-content/uploads/2018/07/Treatment-of-acute-attacks-in-hereditary-angiodema-adult.pdf and https://www.england.nhs.uk/wp-content/uploads/2018/07/Plasma-derived-C1-esterase-inhibitor-for-prophylactic-treatment-of-hereditary-angioesema-types-I-and-II.pdf<br>Newer products covered by NICE recommendations: https://www.nice.org.uk/guidance/ta606 |

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| • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) | Within the UK there is fairly high level consensus on treatment pathways, which are well defined. There is significant international variation in uptake of attenuated androgens in the prophylaxis of HAE, but these medications have significant potential side effect, contraindications and on occasion supply issues. |
| • What impact would the technology have on the current pathway of care? | The new technology would enable patients to access well-tolerated preventative treatment for less severe disease, where currently the only option is attenuated androgens, which often have unacceptable side effects or tolerance issues / are contraindicated. This would apply mainly to those not currently eligible for highly effective prophylactic therapy (C1 or lanadelumab) based on the commissioning criteria, although some patients eligible for those treatments may prefer this technology as it is administered orally. |
| 10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? | |
| • How does healthcare resource use differ between the technology and current care? | The technology, as described above, would offer an effective well-tolerated option where currently one does not exist, is not tolerated or is preferable. |
| • In what clinical setting should the technology be used? (For example, | Specialist / secondary care |

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| primary or secondary care, specialist clinics.) | |
| • What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.) | No / minimal investment required other than cost of the technology itself |
| 11. Do you expect the technology to provide clinically meaningful benefits compared with current care? | Yes |
| • Do you expect the technology to increase length of life more than current care? | Yes – reduced side effects / complications from the other treatment options or leaving the condition untreated / only treated on demand. (please note, a reduction in number of attacks could also mean a reduction in risk of life-threatening attacks) |
| • Do you expect the technology to increase health-related quality of life more than current care? | Yes – enhanced control of disease will improve QoL and ability of eligible patients to be more effective in education / employment |

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| 12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? | More appropriate in those that are needle phobic / have difficulties in parenteral therapies therefore favouring an oral option. Those in whom the other options are contraindicated such as children and adolescents or patients with previous adverse reactions to attenuated androgens.<br>This might be less appropriate in those with extremely severe disease where current prophylaxis (parenteral) may also be appropriate |
| **The use of the technology** | |
| 13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.) | Yes oral administered<br><br>No practical implications |

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| 14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing? | There are likely to be eligibility criteria (mainly from a commissioning point of view) so assessment of suitability based on disease severity mainly<br><br>No additional testing |
| 15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? | Ease of administration as an oral agent |
| 16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it | Yes – only similar alternative currently is attenuated androgen therapy with significant adverse effects and contraindications. Depending on commissioning criteria could benefit patients with moderate to severe activity of disease. Currently effective prophylaxis (non-androgen based) is only accessible to individuals with >2 clinically significant swellings a week – these individuals have to be considered as extremely severe disease. This technology should enable effective therapy for those with moderate to severe disease not meeting the criteria for current prophylaxis |

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| improve the way that current need is met? | |
| • Is the technology a 'step-change' in the management of the condition? | Yes |
| • Does the use of the technology address any particular unmet need of the patient population? | Yes as above and before |
| 17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life? | Side effects are limited with this technology and significantly less than the current oral alternative |
| **Sources of evidence** | |
| 18. Do the clinical trials on the technology reflect current UK clinical practice? | Yes |

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| • If not, how could the results be extrapolated to the UK setting? | |
| • What, in your view, are the most important outcomes, and were they measured in the trials? | Reduction in severity and frequency of attacks with a significant reduction in use of rescue medications |
| • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? | |
| • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | No |
| 19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence? | No |
| 20. Are you aware of any new evidence for the comparator | No |

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| treatment(s) since the publication of NICE technology appraisal guidance [TA606]? | |
| 21. How do data on real-world experience compare with the trial data? | No personal knowledge on this |
| **Equality** | |
| 22a. Are there any potential equality issues that should be taken into account when considering this treatment? | No |
| 22b. Consider whether these issues are different from issues with current care and why. | No |
| **Topic-specific questions** | |

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| 23 Will the technology be used earlier in the pathway than lanadelumab? | Ideally |

**Key messages**

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Effective alternative well-tolerated oral therapy to reduce frequency and severity of HAE swellings
- No currently available alternative that is well-tolerated
- Should be considered for those with moderate to severe disease and not only those with extremely severe disease activity
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Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

## Professional organisation submission

# Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

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

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

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- Your response should not be longer than 13 pages.

| **About you** | |
|---|---|
| 1. Your name | [redacted] |
| 2. Name of organisation | **Royal College of Pathologists** |

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|---|---|
| 3. Job title or position | [redacted] |
| 4. Are you (please tick all that apply): | ☒ an employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ a specialist in the treatment of people with this condition?<br>☒ a specialist in the clinical evidence base for this condition or technology?<br>☐ other (please specify): |
| 5a. Brief description of the organisation (including who funds it). | **The Royal College of Pathologists is a professional membership organisation with charitable status, concerned with all matters relating to the science and practice of pathology.** |
| 4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] | **No** |

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|---|---|
| If so, please state the name of manufacturer, amount, and purpose of funding. | |
| 5c. Do you have any direct or indirect links with, or funding from, the tobacco industry? | **No** |
| **The aim of treatment for this condition** | |
| 6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.) | There are two main aims of treatment:<br>1. To treat acute swelling attacks when they occur to reduce the risk of death (for laryngeal/throat/airway swelling) and morbidity/disability/pain.<br>2. To prevent swelling attacks from happening and allow the patient to have a normal quality of life, as well as reducing psychological morbidity associated with the disease. (Berotralstat is relevant to this aim) |
| 7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by | For prevention (prophylaxis) of swelling attacks – reduction in the frequency of swelling attacks by 50% or more; reduction in the severity/duration of attacks by 50% or more.<br>For treatment of acute swelling attacks – reduction in morbidity and mortality associated with swelling. |

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| x cm, or a reduction in disease activity by a certain amount.) | |
| 8. In your view, is there an unmet need for patients and healthcare professionals in this condition? | Yes, there is an unmet need. There is currently no effective licensed oral preparation for prevention (prophylaxis) of swelling attacks. There are good injectable medications for prophylaxis, but these are restricted to a subset of patients with extremely severe disease.<br>There is also no effective oral preparation for treating swelling attacks when they occur. The only effective medications for treatment of attacks are injections. |
| **What is the expected place of the technology in current practice?** | |
| 9. How is the condition currently treated in the NHS? | Patients are supplied with C1 inhibitor or icatibant for emergency use for treatment of acute swelling.<br>Prophylaxis/preventative treatment is considered in patients who have frequent attacks (usually 1-2 per month or more episodes of swelling). Patients with extremely severe disease (8 or more attacks in 4 weeks) can be offered C1 inhibitor or lanadelumab (if they have not got better with androgens or tranexamic acid) (NSHE commissioning policy). Patient with fewer attacks than this would only be eligible for androgens (unlicensed, current global shortage of danazol, side effects, not suitable for children) or tranexamic acid (ineffective in most patients). |
| • Are any clinical guidelines used in the treatment of the condition, and if so, which? | Yes, there are NHSE commissioning policies for prophylaxis, which determine who qualifies for this.<br>2016 NHSE Clinical Commissioning Policy: Plasma-derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II<br>Lanadelumab is commissioned to the same criteria as the C1 inhibitor policy |
| • Is the pathway of care well defined? Does it vary or are there differences of opinion | Pathway of care is relatively well-defined due to the relatively small number of treatment options available, and the criteria laid out by the commissioning policy.<br>For prevention (prophylaxis), only patients with 8 or more attacks per 4 weeks qualify for C1 inhibitor or lanadelumab (NHSE policy). For patients with fewer than that number of attacks, the available medications for prophylaxis are |

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| between professionals across the NHS? (Please state if your experience is from outside England.) | danazol (unlicensed, current global shortage, androgenic side effects, not suitable for children) and tranexamic acid (generally poor efficacy). (International guidelines do not recommend danazol or tranexamic acid as first line, but UK practice differs from this due to the commissioning policy restricting other prophylactic agents to patients with extremely severe disease)<br>For acute treatment, NHSE commissioning policy allows use of C1 inhibitor or icatibant. All patients are offered this as the swelling attacks can be potentially lethal. |
| • What impact would the technology have on the current pathway of care? | The technology provides patients with a viable oral medication custom designed for prevention of swelling attacks. (The other two options in current use are unlicensed, has potential side effects and is difficult to obtain, or of poor efficacy) |
| 10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? | The technology is an oral medication – so would be offered to any patient with HAE with frequent enough attacks to be considered for prophylaxis. |
| • How does healthcare resource use differ between the technology and current care? | Healthcare resource use may decline with the technology as it reduces the number of swelling attacks that require potential attendance at A&E and hospital for treatment. It may also reduce healthcare resource use in other areas e.g. psychological support due to improved control of illness. |
| • In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.) | Technology should be used within specialist clinics as HAE is a rare condition. |
| • What investment is needed to introduce the technology? (For | Almost no investment required. Technology is an oral medication, and the cohort of patients that would benefit are already being seen in specialist clinics. |

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| example, for facilities, equipment, or training.) | |
| 11. Do you expect the technology to provide clinically meaningful benefits compared with current care? | Yes. An effective licensed oral medication that is available to a wider population of patients with HAE would improve quality of life and reduce burden of other treatments for patients. |
| • Do you expect the technology to increase length of life more than current care? | No |
| • Do you expect the technology to increase health-related quality of life more than current care? | Yes. An effective oral medication to prevent swelling attacks when there is either no effective or available other oral medication would be expected to increase HR-QoL as this would reduce burden of disease and the burden of treating the disease with injectable medications for acute swelling. |
| 12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? | No specific groups. |

| **The use of the technology** | |
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| 13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.) | Likely to be easier to use as technology is an oral medication. If technology reduces the number of swelling attacks a patient has, this means they will use less injectable medications for treatment of acute swelling. |
| 14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing? | Likely that some form of rules would be used to stop treatment if it is ineffective after a certain period of time. This would most likely not include additional testing. |

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| 15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? | Technology may improve psychological morbidity associated with HAE for patients as well as their carers/other family members. |
| 16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? | Yes |
| • Is the technology a 'step-change' in the management of the condition? | Yes, the technology would be the first effective oral medication specifically designed for prevention of HAE attacks. |

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| • Does the use of the technology address any particular unmet need of the patient population? | Yes, it provides an effective oral prophylactic medication for patients with HAE who do not qualify for prophylactic treatment with C1 inhibitor or lanadelumab. This is particularly relevant as the two main oral medications currently in use have limitations i.e. androgens/danazol is unlicensed, have limited global supply, side effects, and is not suitable in children; and tranexamic acid is ineffective in most patients with HAE. |
| 17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life? | Unlikely that side effects of the technology will have a significant effect on management of the patient's condition or quality of life. |
| **Sources of evidence** | |
| 18. Do the clinical trials on the technology reflect current UK clinical practice? | Yes |
| • If not, how could the results be extrapolated to the UK setting? | N/A |
| • What, in your view, are the most important | Reduction in number of swelling attacks – yes, this was measured in the trials. |

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| outcomes, and were they measured in the trials? | Reduction in severity/duration of swelling attacks – this information was collected in the trial, but not in the published paper. |
| • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? | N/A |
| • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | I am not aware of any adverse effects that have come to light subsequently. |
| 19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence? | No |
| 20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA606]? | No |

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| 21. How do data on real-world experience compare with the trial data? | Limited data on RWE available at present. |
| **Equality** | |
| 22a. Are there any potential equality issues that should be taken into account when considering this treatment? | No |
| 22b. Consider whether these issues are different from issues with current care and why. | N/A |
| **Topic-specific questions** | |
| 23 Will the technology be used earlier in the pathway than lanadelumab? | Yes, and/or used in patients who do not qualify for treatment with lanadelumab. |
| **Key messages** | |

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Berotralstat is the first custom-designed oral preventative medication for HAE
- Current oral medication for HAE have significant limitations - danazol/androgens (unlicensed, side effects, global shortage, not suitable in children) and tranexamic acid (ineffective in most patients with HAE)
- Injectable preventative medication (C1 inhibitor and lanadelumab) are restricted to the HAE patients with extremely severe disease (at least 8 episodes of swelling every 4 weeks)
- HAE patients with fewer swelling episodes (7 or fewer attacks per 4 weeks) can still have severe, significant burden of disease, but have no real effective licensed preventative option currently available to them in the UK
- The unmet need is greatest in this subset of HAE patients

Thank you for your time.

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NICE National Institute for Health and Care Excellence

## Professional organisation submission

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- Your response should not be longer than 13 pages.

| **About you** | |
|---|---|
| 1. Your name | [redacted] |
| 2. Name of organisation | **UKPIN (UK Primary Immunodeficiency Network)** |

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| 3. Job title or position | [redacted] |
| 4. Are you (please tick all that apply): | ☒ an employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ a specialist in the treatment of people with this condition?<br>☒ a specialist in the clinical evidence base for this condition or technology?<br>☐ other (please specify): |
| 5a. Brief description of the organisation (including who funds it). | **UKPIN is the professional body for healthcare professionals working in the field of immunodeficiency. It is a registered charity and registered company.** |
| 4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] | **Yes**<br><br>**CSL Behring £35,000, support for the activities of the organisation**<br>**Pharming £5,000, support for the activities of the organisation** |

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| If so, please state the name of manufacturer, amount, and purpose of funding. | |
| 5c. Do you have any direct or indirect links with, or funding from, the tobacco industry? | **No** |
| **The aim of treatment for this condition** | |
| 6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.) | There are two main aims of treatment:<br>1. To treat acute swelling attacks when they occur to reduce the risk of death (for laryngeal/throat/airway swelling) and morbidity/disability/pain.<br>2. To prevent swelling attacks from happening and allow the patient to have a normal quality of life, as well as reducing psychological morbidity associated with the disease. (Berotralstat is relevant to this aim) |
| 7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by | For prevention (prophylaxis) of swelling attacks – reduction in the frequency of swelling attacks by 50% or more; reduction in the severity/duration of attacks by 50% or more.<br>For treatment of acute swelling attacks – reduction in morbidity and mortality associated with swelling. |

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| x cm, or a reduction in disease activity by a certain amount.) | |
| 8. In your view, is there an unmet need for patients and healthcare professionals in this condition? | Yes, there is an unmet need. There is currently no effective licensed oral preparation for prevention (prophylaxis) of swelling attacks. There are good injectable medications for prophylaxis, but these are restricted to a subset of patients with extremely severe disease.<br>There is also no effective oral preparation for treating swelling attacks when they occur. The only effective medications for treatment of attacks are injections. |
| **What is the expected place of the technology in current practice?** | |
| 9. How is the condition currently treated in the NHS? | Patients are supplied with C1 inhibitor or icatibant for emergency use for treatment of acute swelling.<br>Prophylaxis/preventative treatment is considered in patients who have frequent attacks (usually 1-2 per month or more episodes of swelling). Patients with extremely severe disease (8 or more attacks in 4 weeks) can be offered C1 inhibitor or lanadelumab (if they have not got better with androgens or tranexamic acid) (NSHE commissioning policy). Patient with fewer attacks than this would only be eligible for androgens (unlicensed, current global shortage of danazol, side effects, not suitable for children) or tranexamic acid (ineffective in most patients). |
| • Are any clinical guidelines used in the treatment of the condition, and if so, which? | Yes, there are NHSE commissioning policies for prophylaxis, which determine who qualifies for this.<br>2016 NHSE Clinical Commissioning Policy: Plasma-derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II<br>Lanadelumab is commissioned to the same criteria as the C1 inhibitor policy |
| • Is the pathway of care well defined? Does it vary or are there differences of opinion | Pathway of care is relatively well-defined due to the relatively small number of treatment options available, and the criteria laid out by the commissioning policy.<br>For prevention (prophylaxis), only patients with 8 or more attacks per 4 weeks qualify for C1 inhibitor or lanadelumab (NHSE policy). For patients with fewer than that number of attacks, the available medications for prophylaxis are |

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| between professionals across the NHS? (Please state if your experience is from outside England.) | danazol (unlicensed, current global shortage, androgenic side effects, not suitable for children) and tranexamic acid (generally poor efficacy). (International guidelines do not recommend danazol or tranexamic acid as first line, but UK practice differs from this due to the commissioning policy restricting other prophylactic agents to patients with extremely severe disease)<br>For acute treatment, NHSE commissioning policy allows use of C1 inhibitor or icatibant. All patients are offered this as the swelling attacks can be potentially lethal. |
| • What impact would the technology have on the current pathway of care? | The technology provides patients with a viable oral medication custom designed for prevention of swelling attacks. (The other two options in current use are unlicensed, has potential side effects and is difficult to obtain, or of poor efficacy) |
| 10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? | The technology is an oral medication – so would be offered to any patient with HAE with frequent enough attacks to be considered for prophylaxis. |
| • How does healthcare resource use differ between the technology and current care? | Healthcare resource use may decline with the technology as it reduces the number of swelling attacks that require potential attendance at A&E and hospital for treatment. It may also reduce healthcare resource use in other areas e.g. psychological support due to improved control of illness. |
| • In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.) | Technology should be used within specialist clinics as HAE is a rare condition. |
| • What investment is needed to introduce the technology? (For | Almost no investment required. Technology is an oral medication, and the cohort of patients that would benefit are already being seen in specialist clinics. |

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| example, for facilities, equipment, or training.) | |
| 11. Do you expect the technology to provide clinically meaningful benefits compared with current care? | Yes. An effective licensed oral medication that is available to a wider population of patients with HAE would improve quality of life and reduce burden of other treatments for patients. |
| • Do you expect the technology to increase length of life more than current care? | No |
| • Do you expect the technology to increase health-related quality of life more than current care? | Yes. An effective oral medication to prevent swelling attacks when there is either no effective or available other oral medication would be expected to increase HR-QoL as this would reduce burden of disease and the burden of treating the disease with injectable medications for acute swelling. |
| 12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? | No specific groups. |

| **The use of the technology** | |
|---|---|
| 13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.) | Likely to be easier to use as technology is an oral medication. If technology reduces the number of swelling attacks a patient has, this means they will use less injectable medications for treatment of acute swelling. |
| 14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing? | Likely that some form of rules would be used to stop treatment if it is ineffective after a certain period of time. This would most likely not include additional testing. |

| | |
|---|---|
| 15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? | Technology may improve psychological morbidity associated with HAE for patients as well as their carers/other family members. |
| 16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? | Yes |
| • Is the technology a 'step-change' in the management of the condition? | Yes, the technology would be the first effective oral medication specifically designed for prevention of HAE attacks. |

| | |
|---|---|
| • Does the use of the technology address any particular unmet need of the patient population? | Yes, it provides an effective oral prophylactic medication for patients with HAE who do not qualify for prophylactic treatment with C1 inhibitor or lanadelumab. This is particularly relevant as the two main oral medications currently in use have limitations i.e. androgens/danazol is unlicensed, have limited global supply, side effects, and is not suitable in children; and tranexamic acid is ineffective in most patients with HAE. |
| 17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life? | Unlikely that side effects of the technology will have a significant effect on management of the patient's condition or quality of life. |
| **Sources of evidence** | |
| 18. Do the clinical trials on the technology reflect current UK clinical practice? | Yes |
| • If not, how could the results be extrapolated to the UK setting? | N/A |
| • What, in your view, are the most important | Reduction in number of swelling attacks – yes, this was measured in the trials. |

| | |
|---|---|
| outcomes, and were they measured in the trials? | Reduction in severity/duration of swelling attacks – this information was collected in the trial, but not in the published paper. |
| • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? | N/A |
| • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | I am not aware of any adverse effects that have come to light subsequently. |
| 19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence? | No |
| 20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA606]? | No |

| | |
|---|---|
| 21. How do data on real-world experience compare with the trial data? | Limited data on RWE available at present. |
| **Equality** | |
| 22a. Are there any potential equality issues that should be taken into account when considering this treatment? | No |
| 22b. Consider whether these issues are different from issues with current care and why. | N/A |
| **Topic-specific questions** | |
| 23 Will the technology be used earlier in the pathway than lanadelumab? | Yes, and/or used in patients who do not qualify for treatment with lanadelumab. |
| **Key messages** | |

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Berotralstat is the first custom-designed oral preventative medication for HAE
- Current oral medication for HAE have significant limitations - danazol/androgens (unlicensed, side effects, global shortage, not suitable in children) and tranexamic acid (ineffective in most patients with HAE)
- Injectable preventative medication (C1 inhibitor and lanadelumab) are restricted to the HAE patients with extremely severe disease (at least 8 episodes of swelling every 4 weeks)
- HAE patients with fewer swelling episodes (7 or fewer attacks per 4 weeks) can still have severe, significant burden of disease, but have no real effective licensed preventative option currently available to them in the UK
- The unmet need is greatest in this subset of HAE patients

Thank you for your time.

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# Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

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No competing interests to disclose.

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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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## List of abbreviations

| | |
|---|---|
| **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.<br><br>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:<br>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<br>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.<br><br>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]

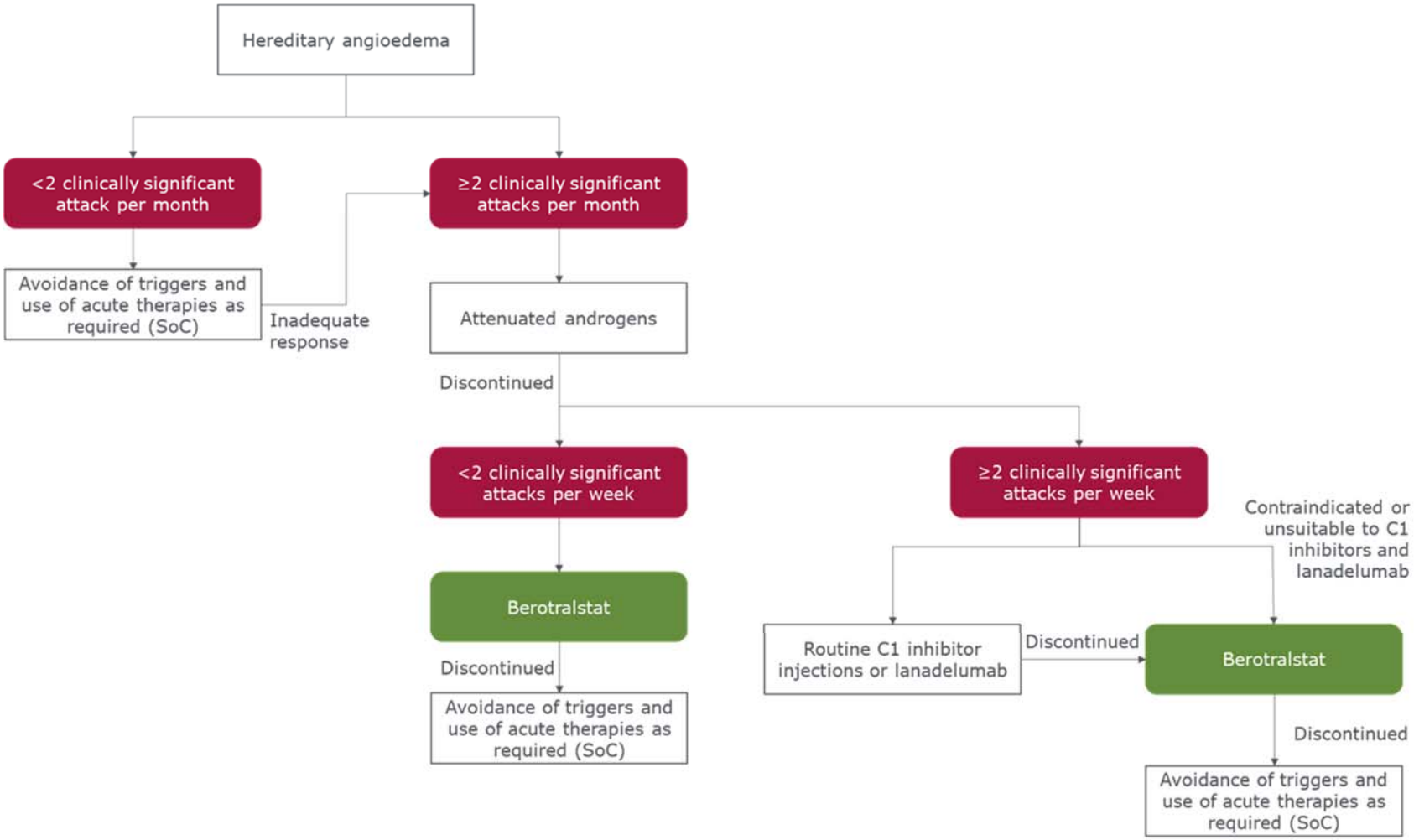
Medical attention is often required during HAE attack episodes and as part of long-term disease monitoring. Treatment options for managing HAE vary from patient to patient, reflective of the clinical heterogeneity of the condition, but generally comprise a) avoidance or treatment of known attack-precipitating 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:<br>• HAE type I or II patients who experience two or more attacks per month who are unsuitable for or refractory to androgens<br>• 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<br>• HAE type I or II patients who experience two or more attacks per month who are unsuitable for or refractory to androgens<br>• 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<br>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. |

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| | | | | 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]<br><br>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.<br><br>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 |

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| | | | | 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:<br>• C1-INHs, attenuated androgens and anti-fibrinolytics<br>• 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:<br>• 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.<br><br>The description of the current UK treatment pathway in the CS positions berotralstat as indicated for<br>• HAE type I or II patients who experience two or more attacks per month who are unsuitable for or refractory to androgens<br>• 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 |

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| | 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.<br><br>• 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. |

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| | | | 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 | |

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| | | | 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.<br><br>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 | |

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| | | | 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:<br>• frequency of angioedema attacks<br>• severity of angioedema attacks<br>• need for acute treatment<br>• mortality<br>• adverse effects of treatment<br>health-related quality of life. | The following outcome measure is not included:<br>• Severity of angioedema attacks<br>Additional outcome measures considered include:<br>• Location of attack (specifically differentiating between Laryngeal, Abdominal and Limb/Peripheral attacks)<br>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.<br>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.<br>The ERG clinical expert's opinion is that robustly defining severity of attack can be difficult as this is |

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| | | | 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 |

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| | 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. |

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| | | | 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]<br><br>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 |

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| | 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. |

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| 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<br>• Severity of angioedema attacks<br>• Need for acute treatment<br>• Mortality<br>• Adverse effects of treatment<br>• Health-related quality of life |
| **All other reported outcomes** | • **Location of attack**<br>• **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=*** | | | ***Placebo; N=*** |
| LSM | | | | |
| Standard error | | | | |
| LSM difference from placebo | | | | |
| 95% CI | | | | |
| P-Value | | | | |
| ***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) | | | | |
| Median | | | | |
| Range | | | | |
| 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).*

*Mode of administration utility benefit*

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] |

# National Institute for Health and Care Excellence

# Centre for Health Technology Evaluation

## ERG report – factual accuracy check and confidential information check

### Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm** on **Monday 8 March 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

**Issue 1**

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| Page 13, section 1.2, first paragraph: berotralstat is misspelt as “berotrolstat” | Replace “berotrolstat” with “berotralstat”. | Corrects typo | The typographical error has been corrected. |

NICE National Institute for Health and Care Excellence

# Technical engagement response form

## Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Wednesday 21 April 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

**Notes on completing this form**

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

**We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

**About you**

| | |
|---|---|
| **Your name** | |
| **Organisation name – stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank) | **BioCryst Pharmaceuticals UK Limited** |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | |

**Key issues for engagement**

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

| Key issue | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| **Key issue 1:** Limited evidence base | **YES** | The ERG is concerned that "the current evidence of clinical effectiveness is based exclusively on a single trial with small sample size and a limited follow-up period".<br><br>APeX-2 is the pivotal study for the use of berotralstat to prevent HAE attack where the ITT population is made up of 40 berotralstat 150mg patients and 40 placebo patients. The proposed positioning of berotralstat in the NICE submission is:<br><br>• HAE type I or II patients who experience two or more attacks per month and are unsuitable or refractory to androgens;<br><br>• 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.<br><br>Given this, the subgroup of APeX-2 patients used to inform the economic model for the NICE submission consists of patients with two or more clinically significant HAE attacks per month at baseline and had received previous treatment with attenuated androgens at baseline (N=35; berotralstat 150mg =17, placebo =18) as this most closely matches the proposed positioning in clinical practice.<br><br>**Company response**<br><br>The issue outlined by the ERG is typical when assessing rare diseases. However, the 80 (proposed positioning: n=35) patients included in APeX-2 represent a similar population size when compared to the sample sizes of studies for other treatments in HAE. The pivotal studies for Cinryze (C1-inhibitor), Haegarda (C1-inhibitor), and Takhzyro (lanadelumab) had 22, 90, and 125 patients, respectively. |

| | | |
|---|---|---|
| | | Furthermore, since the NICE submission in December 2020, long-term efficacy data has become available. An ad-hoc analysis of adjusted monthly attack rates over 96 weeks, demonstrates that the reductions seen in the berotralstat arm in Part 1 of the study are sustained over 96 weeks of treatment. The reduction from baseline in monthly adjusted attack rate for the proposed positioning subgroup (responders only from Month 4 onwards) over 96 weeks is shown in **Error! Reference source not found.**, alongside the reduction in investigator-confirmed attack rate for the same patients over 12 months.<br>[redacted]<br>[redacted] |
| **Key issue 2**: Selection of data used to | **NO** | The ERG is concerned that the percentage reductions from baseline attack rates for berotralstat and SoC patients are derived from the proposed positioning subgroup which consists of a small number of |

Commented [JH1]: New evidence

| | | |
|---|---|---|
| inform the model inputs | | patients (n=35) that is reduced even further when a discontinuation rule is applied (n=8 in the berotralstat arm).<br><br>The ERG believes this leads to uncertainty around the percentage reductions applied and instead proposes using the data from the ITT population (n=80) or the larger subgroup of patients who had two or more clinically significant HAE attacks per month at baseline (n=57) to reduce the uncertainty driven by the small patient numbers.<br><br>**Company response**<br><br>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. This is also the population in which physicians anticipate the most benefit from treatment: patients with ≥2 clinically significant attacks per month and who are unsuitable or refractory to androgens.<br><br>Therefore, using the ITT population of APeX-2 to inform the economic model would mean including patients who would not receive berotralstat in UK clinical practice, undermining the cost-effectiveness evidence that will be used for decision-making.<br><br>Implementing the ERG's suggestion to use the ITT population would amount to arbitrarily increasing the sample size at the cost of 1) efficacy and 2) use of an appropriate patient population.<br><br>As the ERG points out, using the ITT data substantially increases the ICER because, as the clinicians and data demonstrates, berotralstat is more effective in the positioning proposed. To implement the ERG's proposal, would mean taking an ICER that would be regarded as a good use of resources, pushing it to a level that would not be cost-effective while also including a less effective use of berotralstat that neither clinicians nor the company propose, simply to increase the sample size. Consequently, it would be inappropriate to use clinical data including these patients as the basis for decision-making for berotralstat.<br><br>Finally, we believe that rejecting the use of the proposed subgroup positioning on the grounds of small sample size would be inconsistent with precedent set by NICE decisions regarding HAE therapy. In particular, Takhzyro was granted approval in a restricted population based on a small subgroup of patients from the pivotal RCT. |

| | | |
|---|---|---|
| **Key issue 3**: Extrapolation of attack rates beyond the follow-up period of the trial | **YES** | In Part 1 of the APeX-2 trial, patients received either berotralstat or placebo for six months. Data was available for Part 2 of APeX-2 to inform monthly attack rates for berotralstat patients from months 7 to 12. The attack rates beyond 6 months for placebo patients are estimated using the 'last observation carried forward' (LOCF) approach. This assumes that the attack rate remains constant over the remainder of the time horizon at the rate observed in the final observation.<br><br>The ERG is concerned that "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."<br><br>The ERG prefers using an average of the monthly attack rates across months 0-6 for placebo patients, as this accounts for the observed variation in placebo attack rates.<br><br>**Company response**<br><br>Clinical experts at a recent advisory board stated that they believed that patients in APeX-2 may have experienced a placebo effect, which is in line with findings they have observed from other trials in HAE which have shown a similar pattern in attack rates for placebo patients.[1,2]<br><br>The placebo effect may be as a result of a decreased sense of stress and anxiety about having an attack. Clinicians at a recent advisory board confirmed that stress and anxiety are known factors which increase attack rates in HAE patients.[2] APeX-2 was a double-blinded trial, in which patients may have believed they were randomised to receive berotralstat when in actuality they were treated with placebo, leading to reduced stress and anxiety, which is reflected in the short-term reduced attack rate.<br><br>The experts advised that after a few months, placebo patients would begin to suspect that they were not on active treatment as their attacks had not significantly decreased. After this point, the placebo effect would begin to wear off.[2] This aligns with the observation shown in Table 1 of reduced attack rates in Months 1 to 5 of the trial, which had worn off by Month 6. |

**Commented [JH2]:** New evidence

**Commented [JH3]:** New evidence

**Table 1: Attack rates from Month 0 to 6 in the proposed positioning subgroup[a]**

| Treatment | Mean number of attacks | | | | | | |
|---|---|---|---|---|---|---|---|
| | Baseline | Month 1 | Month 2 | Month 3 | Month 4 | Month 5 | Month 6 |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Placebo | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

[a] The proposed positioning is patients with two or more clinically significant HAE attacks per month at baseline and had received previous treatment with attenuated androgens at baseline

Furthermore, clinical experts advised that patients typically experience an improved level of overall care in a clinical trial than in clinical practice, which may have influenced the reduction in attack rate for placebo patients despite the lack of prophylactic therapy.[2]

The clinical experts advised that once the placebo effect had worn off, attack rates would be expected to revert to baseline levels and remain at that level.[2] As such, in keeping with the clinical feedback received, the company believes it reasonable to amend the base case economic analysis, such that after Month 6, the attack rate for SoC patients reverts to baseline for the remainder of the time horizon.

The Company also believes the experts view that the patients in APeX-2 experienced a placebo effect that led to observed reductions in months 1 to 5 of the trial, which had worn off by month 6. The observed variation explanation of the placebo attack rates suggested by the ERG is unlikely, given that over the six months of Part 1 of APeX-2, all but one of the placebo observations reported a decrease in mean number of attacks compared to baseline (Table 1). This further supports the argument of a placebo effect.

In contrast to this, the sustained reduction in the attack rate as shown in the ad-hoc 96-week analysis (**Error! Reference source not found.**) indicates that the placebo effect is not the cause of the i mprovement in attack rates in the berotralstat arm as the treatment effect is maintained far longer than would be plausible if caused by a placebo effect.

**Commented [JH4]:** New evidence

**Commented [JH5]:** New evidence

| | | |
|---|---|---|
| | | Indeed, the LOCF approach in the economic model based on investigator adjusted attack may be a conservative assumption compared to LOCF considering the adjusted attack rate (**Error! Reference s ource not found.**). The most recent trial evidence demonstrates that berotralstat may be more efficacious than is observed at 12 months, with a 95% decrease from baseline in adjusted attack rate observed at Month 24, in comparison to the 85% reduction in investigator-confirmed attack rate used from Month 12 onwards in the LOCF analysis.<br><br>Nevertheless, since the 24-month data is based on a subset of patients who have reached that 12 month timepoint and is based on adjusted attack rate rather than investigator-confirmed attack rate, it has not been used in the economic model. It is however useful for validation of extrapolation methods for the 12-month data.<br><br>Therefore, there are two potential options for extrapolating the reduction in attack rate beyond Month 12:<br><br>• LOCF from Month 12<br>o Based on **Error! Reference source not found.**, this would be a conservative estimation w hen compared to using LOCF from Month 24, and may actually underestimate the long-term efficacy of berotralstat.<br><br>• Average reduction in attack rate over Months 4-12<br>o This leads to a more conservative estimation of the long-term efficacy than using LOCF from Month 12 or Month 24, and may underestimate the long-term efficacy of berotralstat.<br><br>To address the ERG's concerns, the company has adjusted the base case analysis such that the average reduction in attack rate over Months 4-12 is used from Month 12 onwards. This is the most conversative option of the two available, and in light of the 24-month data, is likely to be an underestimate of the cost- |

**Commented [JH6]:** New evidence

effectiveness of berotralstat. The company also accepts the ERG's suggestion to use a pooled baseline attack rate between the arms and a separate baseline attack rate for berotralstat responders.

The impact of applying the changes to both the berotralstat and SoC attack rates on the base case ICER originally submitted to NICE is shown in Table 2, while the company's revised base case including a further change based on Key Issue 6 is shown in Table 3.

**Table 2: Impact on the original base case ICER of applying changes to berotralstat and SoC attack rates**

Commented [JH7]: New analyses

| | Berotralstat | SoC |
|---|---|---|
| Total costs (£) | XXXXXXX | XXXXXXX |
| Total LYG | XXXXX | XXXXX |
| Total QALYs | XXXXX | XXXXX |
| Incremental costs (£) | XXXXX | - |
| Incremental LYG | XXXX | - |
| Incremental QALYs | XXXX | - |
| ICER (£/QALY) | £62,285 | - |

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

**Table 3: Company revised base case (updated based on Key Issue 3 and 6)**

| | Berotralstat | SoC |
|---|---|---|
| **Company revised base case** | | |
| Total costs (£) | XXXXXXX | XXXXXXX |
| Total LYG | XXXXX | XXXXX |

| | | | | |
|---|---|---|---|---|
| | | Total QALYs | XXXXX | XXXXX |
| | | Incremental costs (£) | XXXXX | - |
| | | Incremental LYG | XXXX | - |
| | | Incremental QALYs | XXXX | - |
| | | ICER (£/QALY) | £69,908 | - |
| **Key issue 4:** Characterizing uncertainty around the ICER (PSA) | **YES** | The ERG is concerned about the characterisation of uncertainty around the estimated ICER. The ERG stated in their report that "The original probabilistic sensitivity analysis (PSA) 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.".<br><br>**Company response**<br><br>In the Clarification Questions (B.16), the ERG requested the company to use actual standard errors from the trial data for the application of the PSA, but these introduced levels of variation which were too extreme for any true impact of uncertainty to be identified.<br><br>It is important to capture the true variability of the inputs within the economic model to best understand the impact of the level of uncertainty. The Company appreciates that the small patient numbers in the model do lead to variability in the PSA. Given this, a scenario has been conducted where the level of the variability in the reduction in attack rates used in the PSA has been increased to 20% to demonstrate that the model is less sensitive to increases in variation of the key parameters than the ERG suggest.<br><br>The results show that the ICER is not very sensitive to increases in variation and does in fact slightly improve when variation is increased. | | |

To address the ERG's concerns, the company has adjusted the base case probabilistic ICER to have a 20% level of variability.

**Table 4: Impact of using different levels of variation in the PSA on the company's revised base case ICER**

| | Berotralstat | SoC |
|---|---|---|
| **PSA: 10%** | | |
| Total costs (£) | XXXXXXX | XXXXXXX |
| Total LYG | XXXXX | XXXXX |
| Total QALYs | XXXXX | XXXXX |
| Incremental costs (£) | XXXXX | - |
| Incremental LYG | XXXX | - |
| Incremental QALYs | XXXX | - |
| ICER (£/QALY) | £69,908 | - |
| **PSA: 20%** | | |
| Total costs (£) | XXXXXXX | XXXXXXX |
| Total LYG | XXXXX | XXXXX |
| Total QALYs | XXXXX | XXXXX |
| Incremental costs (£) | XXXXX | - |
| Incremental LYG | XXXX | - |

Commented [JH8]: New analyses

| | | |
|---|---|---|
| | | Incremental QALYs \| XXXX \| -<br>ICER (£/QALY) \| £67,744 \| -<br>Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years; SD, standard deviation; SoC, standard of care |
| **Key issue 5:** The use of utility values from a published study in preference to EQ-5D data collected in the APeX-2 trial | **YES** | EQ-5D-5L data were collected in APeX-2 but were not used to estimate utility values in the model as the data is suboptimal, due to the timing of data collection not aligning with the onset of HAE attacks.<br>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".<br>**Company response**<br>The following formula, derived by Ara and Brazier, was used to calculate the age-adjusted utility values for a member of the general population with the same demographics of a member of the subgroup of interest and a member of the ITT population of APeX-2:[3]<br>$$EQ-5D = 0.9508566 + 0.0212126 * male - 0.00002587 * age - 0.0000332 * age^2$$<br>The age-adjusted utility values for members of the general population with the same demographics as the subgroup of interest and ITT population of APeX-2 were calculated as [redacted] and 0.888617. APeX-2 data from both populations suggests that attack-free HAE patients, and sometimes even those experiencing an attack, would have better quality of life than a member of the general population.<br>Table 5 and Table 6 show the utility scores of patients in subgroup of interest and ITT population of the APeX-2 trial, respectively, split by whether their assessment coincided with an HAE attack. Detailed EQ-5D data for the proposed positioning subgroup has been provided in the Clarification questions response document (Table 16). |

**Table 5: Utility values in proposed positioning subgroup[a]**

| Timepoint | Attack is ongoing at time of assessment | Attack is *not* ongoing at time of assessment |
|---|---|---|
| Baseline | [redacted] | [redacted] |
| Week 4 | [redacted] | [redacted] |
| Week 8 | [redacted] | [redacted] |
| Week 12 | [redacted] | [redacted] |
| Week 18 | [redacted] | [redacted] |
| Week 24 | [redacted] | [redacted] |
| **Average** | [redacted] | [redacted] |

[a] The proposed positioning is patients with two or more clinically significant HAE attacks per month at baseline and had received previous treatment with attenuated androgens at baseline

**Table 6: Mean EQ-5D data from the trial based on the ITT population**

Commented [JH9]: New evidence

| Timepoint | Attack is ongoing at time of assessment | Attack is not ongoing at time of assessment |
|---|---|---|
| Baseline | XXXXX | XXXXX |
| Week 4 | XXXXX | XXXXX |
| Week 8 | XXXXX | XXXXX |
| Week 12 | XXXXX | XXXXX |
| Week 18 | XXXXX | XXXXX |

| | | |
|---|---|---|
| Week 24 | XXXXX | XXXXX |
| **Average** | XXXXX | XXXXX |

These results suggest that HAE patients have better HRQoL than members of the general population at several timepoints, both when attack-free and when experiencing an attack, and that over the course of the trial, attack-free patients had an average utility score higher than a member of the general population with the same demographics.

Clinical experts in a recent advisory board stated that it is not clinically plausible that a HAE patient, even when attack-free, would have better quality of life than a member of the general population.[2] For example, attack-free patients will experience fear and anxiety about having unexpected HAE attacks, while patients having attacks experience debilitating, disabling, and symptoms which can result in death from asphyxiation due to laryngeal swelling[4]. This aligns with the findings of a patient survey conducted by BioCryst in which, patients reported feeling anxiety, depression, and feelings of being misunderstood, frustration and isolation.

Commented [JH10]: New evidence

Analysis of the EQ-5D results from the ITT population of APeX-2 show similar results to the subgroup of interest, suggesting that issues with use of EQ-5D data were not solely due to the limited sample size of the subgroup.

Due to unsuitability of the APeX-2 HRQoL data, the Company used utility values presented by Nordenfelt *et al*. (2014)[5] which reported the results of a retrospective survey of patients from a Swedish registry. The results of this study align with those of the TTO study conducted by BioCryst which was specifically designed to obtain utility values for both patients who are experiencing HAE attacks and those who are attack-free. A scenario using the TTO values was included in the submission dossier (Section 3.8.3).

Nordenfelt *et al*. (2014)[5] utility values were presented in the company submission dossier, and given the issues identified with APEX-2 utilities, were deemed the most robust EQ-5D-5L utility estimates for time spent attack-free as well as time spent experiencing an attack. Furthermore, these utility values have

| | | |
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| | | previously been accepted by NICE in the appraisal of lanadelumab in HAE and were utilised in the evidence reported published by the Institute for Clinical and Economic Review in the US, validating their appropriateness for NICE decision making.[1,6] |
| **Key issue 6:** The inclusion of carer disutility in the base case analysis | **YES** | A caregiver disutility value of [redacted] is applied in the economic model which is reflective of 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.<br><br>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."<br><br>**Company response**<br><br>There is a significant burden experienced by caregivers of HAE patients due to the substantial amount of time spent offering both physical and emotional support as well as shared anxiety over attacks.<br><br>Many HAE attacks are very disabling, with patients confined to bed for hours or days on end or left without use of their limbs. Combined with symptoms such as nausea and diarrhoea, this amounts to a high burden on caregivers in terms of physical support. Due to the hereditary nature of the disease, many carers are also HAE patients, who not only fear for their own attacks, but also the attacks of those they are providing care to as many HAE patients have experienced a relative who has died from a HAE attack. This fear of death from an attack was highlighted by clinical experts at an advisory board, who agreed it was common and a key component of attack-related anxiety.<br><br>The NICE reference case stipulates that caregiver burden should be included in the base case analysis, specifically 'all direct health effects, whether for patients or, when relevant, carers' should be considered. As such, it is inappropriate to model the effects of HAE without taking caregiver burden into account, when it clearly exists and can be quantified in the economic model. |

**Commented [JH11]:** New evidence

The disutility of [redacted], while substantial, is only applied in the economic model when patients are experiencing an attack. As the average duration of attacks applied in the economic model is 31.3 hours for berotralstat patients and 33.1 hours for SoC patients, and there are 672 hours per 28-day cycle, this means that the vast majority of the time, no disutility is applied. Given the nature of anxiety surrounding HAE, this is already a conservative assumption. Furthermore, the ERG is concerned as the QALY reduction in the SoC arm is higher than in the berotralstat arm. Caregiver disutility is less in the berotralstat arm because the disutility is driven by the attack rate. Given that patients in the berotralstat arm have reduced attacks compared to the SoC arm, it is correct and appropriate that carer disutility reduces QALYs in the SoC arm of the model more than in the berotralstat arm.

In order to address the ERG's concern that the difference in caregiver utility has been overestimated, the company has amended the base case analysis such that caregiver disutility is only applied to 52.4% of attacks. This is in line with the proportion of patients who reported receiving assistance from a caregiver during their last attack in Aygören-Pürsün et al. (2014).[7]

Commented [JH12]: New evidence

The impact of this analysis on the original base case ICER submitted to NICE are presented in Table 7, while the revised base case ICER including this change is displayed in Table 8.

**Table 7: Impact on the original base case ICER of applying changes to caregiver disutility**

| | Berotralstat | SoC |
|---|---|---|
| Total costs (£) | XXXXXXXX | XXXXXXXX |
| Total LYG | XXXXX | XXXXX |
| Total QALYs | XXXXX | XXXXX |
| Incremental costs (£) | XXXXXX | - |
| Incremental LYG | XXXX | - |

| | | |
|---|---|---|
| Incremental QALYs | XXXX | - |
| ICER (£/QALY) | £23,372 | - |

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

**Table 8: Company revised base case (updated based on Key Issue 3 and 6)**

| | Berotralstat | SoC |
|---|---|---|
| **Company revised base case** | | |
| Total costs (£) | XXXXXXXX | XXXXXXXX |
| Total LYG | XXXXX | XXXXX |
| Total QALYs | XXXXX | XXXXX |
| Incremental costs (£) | XXXXXX | - |
| Incremental LYG | XXXX | - |
| Incremental QALYs | XXXX | - |
| ICER (£/QALY) | £69,908 | - |

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

**Commented [JH13]:** New analyses

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| **Key issue 7:** The attack costs applied in each arm | **YES** | In the Company submission, the cost per attack is higher in the SoC arm due to the reduced need for acute treatment 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." |

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| | | **Company response**<br><br>Table 9 below demonstrates that use of acute treatments in the berotralstat and SoC arms of APeX-2 is consistent in our subgroup and the ITT and ≥2 attacks at baseline populations. As such, the reduction in attack costs for berotralstat patients observed in the subgroup is not a chance finding due to a small sample size.<br><br>Additionally, the cost per attack per treatment was estimated as per the observed data in APeX-2. The percentage reduction in on-demand medication use with berotralstat (54% relative to placebo) was greater than the reduction in attack rate (44% relative to placebo). Additionally, the percentage of HAE attacks retreated with on-demand medication was lower for the 150mg group than the placebo group (17% versus 27%). Combined, this suggests that berotralstat reduces attack severity compared to SoC.<br><br>Clinical experts at a recent advisory board concluded that the reduction in need for multiple administrations of acute treatment in the berotralstat arm was due to a reduction in the severity of attacks - a suitable proxy for this is how much medication was needed to bring the attack under control.[2] It is for this reason that SoC patients are associated with higher acute treatment costs in the model.<br><br>The experts gave a clear rationale for why placebo patients would be more likely to require multiple administrations of acute treatment than patients receiving prophylactic treatment for HAE:[2]<br><br>• The experts consulted explained that how quickly and how far attacks develop will depend on the background levels of kallikrein and bradykinin that patients have.<br><br>• Patients on effective prophylaxis will have lower background levels of bradykinin production, making it easier to either avert clinically manifested attacks or limit their severity and duration.<br><br>• It was explained that the same mechanism of denying the contact system the opportunity to amplify itself in an exponential way underlay the finding that the earlier an HAE attack is treated, the less severe and long lasting it is likely to become. |

**Commented [JH14]:** New evidence

**Table 9: Proportion of attacks treated with acute treatment**

| | ≥2 attacks and prior androgen | | ≥2 attacks | | ITT | |
|---|---|---|---|---|---|---|
| Variable | Berotralstat | SoC | Berotralstat | SoC | Berotralstat | SoC |
| Proportion treated with 1 dose | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx |
| Proportion treated with 2 doses | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx |
| Proportion treated with 3 doses | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx |
| Proportion treated with 4 doses | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx |
| Proportion treated with 5 doses | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx |
| Proportion treated with 6 doses | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx |
| Proportion treated | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx |

**Commented [JH15]:** New evidence in the ≥2 attacks and ITT columns

| | | | | | | | | |
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| | | with 7 doses | | | | | | |
| | | Proportion treated with 10 doses | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx | Xxxx |

**Additional issues**

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

| Issue from the ERG report | Relevant section(s) and/or page(s) | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Additional issue 1: **Attack resource use costs** | **Section 4.2.8, Subsection: 'Health state unit costs and resource use', Page 58, Paragraph 2.** | **NO** | The ERG is concerned 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". They again report that "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."<br><br>**Company response**<br><br>Resource use is split by attack location which is a proxy for severity. The use of these resource by HAE patients was determined through discussions with UK clinical experts during an advisory board meeting. More patients in the SoC arm experienced a laryngeal attack than the berotralstat arm (6% versus 5%). This was a key driver in the increased resource use requirements for HAE attacks which led to the different resource use costs for each treatment.<br><br>Clinical experts at an advisory board agreed that they would expect SoC patients to use more healthcare resources than patients receiving active prophylactic treatment, for the same reasons given in the response to key issue 7, namely that how quickly and how far attacks develop will depend on the background levels of kallikrein and bradykinin that patients have.[2] Patients on effective prophylaxis will have lower background levels of bradykinin production, making it easier to either avert clinically manifested attacks or limit their severity and duration.<br><br>The same mechanism of denying the contact system the opportunity to amplify itself in an exponential way underlay the finding that the earlier an HAE attack is treated, the less severe and long lasting it is likely to |

| | | | |
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| | | | become. The experts thus interpreted the reduction in resource use in the berotralstat arm as being due to a reduction in the severity of attacks and considered a suitable proxy for this to be how much medication was needed to bring the attack under control. It is for this reason that it is appropriate that SoC patients are associated with higher resource use costs in the model. |

**Commented [JH16]:** New evidence

<table>
<tr>
<td>Additional issue 2: Uncertainty around the number of attacks observed</td>
<td>Section 4.2.8, Subsection: ‘Health state unit costs and resource use’, Page 58, Paragraph 3.</td>
<td>YES</td>
<td>
The ERG felt that there was a discrepancy between the number of attacks observed in the response to the clarification questions.<br><br>
In Table 13 of the Company response (Table 10 below), the total number of attacks is [redacted] in the berotralstat and SoC arms respectively.<br><br>
Table 10: Location of attacks observed in the APeX trials for patients experiencing ≥2 attacks per month and previous use of androgens at baseline
<table>
<tr><th rowspan="2">Attack location</th><th colspan="2">Total number of attacks</th></tr>
<tr><th>Berotralstat; N=17</th><th>SoC; N=18</th></tr>
<tr><td>Abdominal/thoracic</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Limb/other</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Laryngeal</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: SoC, standard of care<br><br>
This is inconsistent with Table 19 of the response document (Table 11 below) where the number of attacks requiring treatment are [redacted] respectively.<br><br>
Table 11: Administration of acute therapies observed in APeX-2 for patients experiencing ≥2 attacks per month and previous use of androgens at baseline
<table>
<tr><th>Variable</th><th>Berotralstat; N=17</th><th>SoC; N=18</th></tr>
<tr><td>Attacks treated</td><td></td><td></td></tr>
<tr><td>Number of attacks treated with any acute therapy</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
</tr>
</table>

Abbreviations: SoC, standard of care

Company response

In Table 13 of the Company response (Table 10 above), we include abdominal/thoracic, limb/other and laryngeal attacks, which as the ERG states totals [redacted] in the berotralstat and SoC arms respectively.

In Table 19 of the company response (Table 11 above), these numbers differ for two reasons. Firstly, this refers to only attacks which have been treated. Table 13 refers to total attacks (treated and not treated). Secondly, the attack numbers used in Table 19 of the company response are investigator-confirmed. Laryngeal attacks are not included as they were only considered as a post-hoc analysis. Instead, mixed-location attacks are included.

The sum of abdominal/thoracic, limb/other and mixed-location investigator-confirmed treated attacks, equals [redacted] attacks for berotralstat and SoC, respectively

**Table 12: Alternative number of treated attacks per attack location**

| Attack location | Total number of treated attacks | |
|---|---|---|
| | Berotralstat; N=17 | SoC; N=18 |
| Abdominal/thoracic | [redacted] | [redacted] |
| Limb/other | [redacted] | [redacted] |
| Mixed-location | [redacted] | [redacted] |

Abbreviations: SoC, standard of care

**Summary of changes to the company's cost-effectiveness estimate(s)**

**Company:** If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

**Table 13: Summary of changes to the company's cost-effectiveness estimates**

| Key issue(s) in the ERG report that the change relates to | Company's base case before technical engagement | Change(s) made in response to technical engagement | Impact on the company's base-case ICER |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Key issue 3**: Extrapolation of attack rates beyond the follow-up period of the trial | LOCF was used as the method of extrapolating the reduction in attack rate beyond the trial period in both the berotralstat and SoC arms. | The reduction in attack rate from baseline beyond 12 months for berotralstat patients uses a weighted average of the observations in Months 4-12.<br>The reduction in attack from baseline beyond 6 months for SoC patients is set to 0%, as it is assumed that patients who are not receiving active treatment will not experience a placebo effect. | Previous base case ICER: £21,129<br>Updated ICER: £62,285<br>Change: +£41,156 |
| **Key Issue 4** | The level of the variability in the reduction in attack rates used in the PSA was set to 10% | The level of the variability in the reduction in attack rates used in the PSA has been increased to 20% and applied in the company's preferred base case following technical engagement | Previous PSA ICER: £21,137<br>Updated PSA ICER: £67,744<br>Change: +£46,607 |
| **Key issue 6:** The inclusion of carer disutility in the base case analysis | A caregiver disutility value of [redacted] was applied to all HAE attacks. | A caregiver disutility value of [redacted] is applied to 52.4% of attacks, in line with the proportion of patients who reported receiving assistance from a caregiver during their last attack in Aygören-Pürsün *et al.* (2014).[7] | Previous base case ICER: £21,129<br>Updated ICER: £23,372<br>Change: +£2,243 |

**Commented [JH17]:** New analysis

**Commented [JH18]:** New analysis

**Commented [JH19]:** New analysis

| | | | |
|---|---|---|---|
| Company's preferred base case following technical engagement | Incremental QALYs: [redacted] | Incremental costs: £[redacted] | Previous base case ICER: £21,129<br><br>Updated base case ICER: £69,908<br><br>Change: +£48,779 |

**References**

(1) NICE. Lanadelumab for Preventing Recurrent Attacks of Hereditary Angioedema. 2019.
(2) *UK Advisory Board. BioCryst Data on File. 29 March 2021*.
(3) Ara, R.; Brazier, J. E. Populating an Economic Model with Health State Utility Values: Moving toward Better Practice. *Value Health* **2010**, *13* (5), 509–518. https://doi.org/10.1111/j.1524-4733.2010.00700.x.
(4) Bork, K.; Hardt, J.; Witzke, G. Fatal Laryngeal Attacks and Mortality in Hereditary Angioedema Due to C1-INH Deficiency. *J. Allergy Clin. Immunol.* **2012**, *130* (3), 692–697. https://doi.org/10.1016/j.jaci.2012.05.055.
(5) Nordenfelt, P.; Dawson, S.; Wahlgren, C.-F.; Lindfors, A.; Mallbris, L.; Björkander, J. Quantifying the Burden of Disease and Perceived Health State in Patients with Hereditary Angioedema in Sweden. *Allergy Asthma Proc* **2014**, *35* (2), 185–190. https://doi.org/10.2500/aap.2014.35.3738.
(6) ICER. *Prophylaxis of Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value*; Institute for Clinical and Economic Review, 2018.
(7) Caballero, T.; Aygören-Pürsün, E.; Bygum, A.; Beusterien, K.; Hautamaki, E.; Sisic, Z.; Wait, S.; Boysen, H. B. The Humanistic Burden of Hereditary Angioedema: Results from the Burden of Illness Study in Europe. *Allergy Asthma Proc* **2014**, *35* (1), 47–53. https://doi.org/10.2500/aap.2013.34.3685.

# Appendix L: Results of the economic analysis following post-ERG report revisions and PAS price revisions

### *J.1.1 Base case results*

When using the revised PAS price of [redacted] per 28-capsule pack of berotralstat, berotralstat generates [redacted] incremental QALYs for [redacted] incremental costs over a lifetime horizon compared with SoC, resulting in berotralstat dominating SoC.

**Table 1: Base-case incremental cost-effectiveness analysis results**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER versus baseline (£/QALY) | ICER incremental (£/QALY) |
|---|---|---|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | [redacted] | - | - | - | - | - |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Berotralstat dominant | Berotralstat dominant |

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

### *J.1.1 Probabilistic sensitivity analysis*

The mean values for total costs, LYs, QALYs, and incremental cost per QALY gained for berotralstat versus SoC for the sub-population of interest generated through 10,000 simulations of the PSA are presented in Table 2. In the PSA, berotralstat generates [redacted] incremental QALYs and [redacted] incremental costs over a lifetime horizon compared with SoC, resulting in berotralstat dominating SoC.

The corresponding ICEP and CEAC are presented in Figure 1 and Figure 2, respectively. At a WTP threshold of £30,000 berotralstat had a [redacted]% probability of being cost-effectiveness compared to SoC.

**Table 2: Mean PSA results**

| Technologies | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER incremental (£/QALY) |
|---|---|---|---|---|---|
| SoC | [redacted] | [redacted] | - | - | - |
| Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | Berotralstat dominant |

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SoC, standard of care

**Figure 1: Incremental cost effectiveness plane**

**Figure 2: Cost effectiveness acceptability curve**

### *J.1.1 One-way sensitivity analysis*

The OWSA tornado diagram presenting the top 15 most sensitive parameters for the sub-population of interest is presented in Figure 3. Table 3 presents the OSWA results for these 15 parameters. The model was most sensitive to the baseline attack rate for SoC, the proportion of attacks treated for SoC, and the price of berotralstat per cycle.

**Figure 3: Tornado diagram for the OWSA**

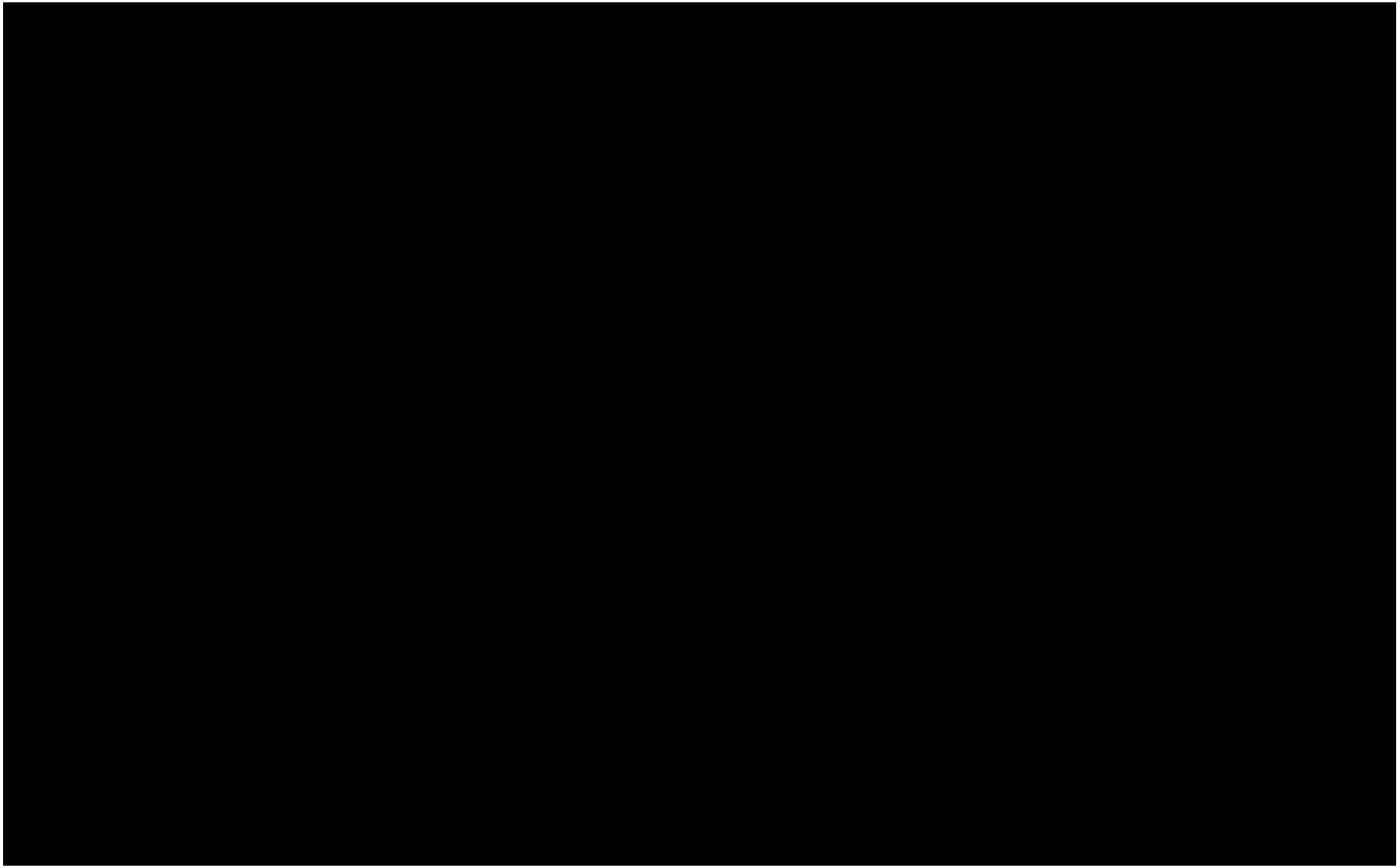

**Table 3: OWSA results for the 15 parameters that contribute the largest difference to the ICER**

| Parameter | Lower bound (£) ICER | Upper bound (£) ICER | Max Difference (£) ICER |
|---|---|---|---|
| Baseline attack rate (SoC) | £236,839 | -£271,777 | £314,713 |
| SoC: proportion of attacks treated | £180,583 | -£190,247 | £258,457 |
| Berotralstat price per cycle | -£276,040 | £120,292 | £198,166 |
| Berotralstat compliance | -£276,040 | -£50,379 | £198,166 |
| SoC: Firazyr cost per attack | £85,413 | -£241,161 | £163,287 |
| SoC: proportion of attacks treated with Firazyr single dose | -£8,051 | -£147,697 | £69,823 |
| SoC: proportion of attacks treated with Firazyr single dose | -£8,051 | -£147,697 | £69,823 |
| SoC: Berinert cost per attack | -£32,921 | -£122,827 | £44,953 |
| Berotralstat: proportion of attacks treated | -£122,591 | -£55,761 | £44,717 |
| SoC: proportion of patients requiring second dose of Firazyr | -£33,891 | -£121,857 | £43,983 |
| SoC: proportion of attacks treated with Berinert single dose | -£34,419 | -£121,329 | £43,455 |
| SoC: proportion of attacks treated with Berinert single dose | -£34,419 | -£121,329 | £43,455 |
| Baseline attack rate (berotralstat) | -£118,157 | -£34,450 | £43,424 |
| SoC: mean attack duration (hours) | -£114,642 | -£58,963 | £36,768 |
| Patient weight (kg) | -£44,900 | -£102,135 | £32,974 |

Abbreviations: ICER, incremental cost effectiveness ratio; kg, kilograms; SoC, standard of care

NICE National Institute for Health and Care Excellence

## Clinical expert statement & technical engagement response form

# Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

**Information on completing this form:**

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Wednesday 21 April 2021**.

**Completing this form**

**Part 1** can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

**Important information on completing this expert statement**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

| **PART 1 – Treating a patient with acute attacks of hereditary angioedema and current treatment options** | |
|---|---|
| **About you** | |
| 1. Your name | **Patrick Yong** |
| 2. Name of organisation | **UKPIN, RCPath** |
| 3. Job title or position | **Consultant Immunologist** |
| 4. Are you (please tick all that apply): | ☒ an employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ a specialist in the treatment of people with acute attacks of hereditary angioedema?<br>☒ a specialist in the clinical evidence base for acute attacks of hereditary angioedema or technology?<br>☐ other (please specify): |
| 5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ yes, I agree with it<br>☐ no, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ other (they didn't submit one, I don't know if they submitted one etc.) |

| | |
|---|---|
| 6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.) | ☒ yes |
| 7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **No links to the tobacco industry** |
| **The aim of treatment for acute attacks of hereditary angioedema** | |
| 8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.) | |
| 9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, | |

| | |
|---|---|
| or a reduction in disease activity by a certain amount.) | |
| 10. In your view, is there an unmet need for patients and healthcare professionals in acute attacks of hereditary angioedema? | |
| **What is the expected place of the technology in current practice?** | |
| 11. How is the condition currently treated in the NHS? | |
| • Are any clinical guidelines used in the treatment of the condition, and if so, which? | |
| • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) | |

| | |
|---|---|
| • What impact would the technology have on the current pathway of care? | |
| 12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? | |
| • How does healthcare resource use differ between the technology and current care? | |
| • In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.) | |
| • What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.) | |
| 13. Do you expect the technology to provide clinically meaningful | |

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| benefits compared with current care? | |
| • Do you expect the technology to increase length of life more than current care? | |
| • Do you expect the technology to increase health-related quality of life more than current care? | |
| 14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? | |
| **The use of the technology** | |
| 15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant | |

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| treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.) | |
| 16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing? | |
| 17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? | |
| 18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it | |

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| improve the way that current need is met? | |
| • Is the technology a 'step-change' in the management of the condition? | |
| • Does the use of the technology address any particular unmet need of the patient population? | |
| 19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life? | |
| **Sources of evidence** | |
| 20. Do the clinical trials on the technology reflect current UK clinical practice? | |
| • If not, how could the results be extrapolated to the UK setting? | |

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| • What, in your view, are the most important outcomes, and were they measured in the trials? | |
| • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? | |
| • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | |
| 21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence? | |
| 22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA606]? | |

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| 23. How do data on real-world experience compare with the trial data? | |
| **Equality** | |
| 24a. Are there any potential equality issues that should be taken into account when considering this treatment? | |
| 24b. Consider whether these issues are different from issues with current care and why. | |

| PART 2 – Technical engagement questions for clinical experts | |
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| **Issues arising from technical engagement** | |
| We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.<br>The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.<br>For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee. | |
| **Key issue 1:** Limited evidence base<br><br>1) Do you have any general comments on this issue? | Due to the rarity of HAE, it is generally difficult to do very large trials in the disease condition. |
| 2) Provided the small sample size of the trial and the company's proposed positioning, do you consider the evidence from the trial to be representative of HAE in UK clinical practice? | Evidence from the trial would be representative of HAE in UK clinical practice, as patients in the trial would be a group of patients with currently very limited options for prophylactic treatment, and berotralstat would be something we would consider using. However, there will also be a significant cohort of patients not on previous androgens previously where berotralstat may potentially be beneficial. This is likely to increase in view of the supply issues with androgens i.e. there is a current directive not to start new patients on androgens due to supply shortages. |

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| 3) Is 24 months follow-up appropriate to capture key outcomes and inform key clinical effectiveness parameters? | 24 months should be long enough to capture the key information necessary. It is unlikely that going on for longer would generate much more new information. Ideally one would have preferred to have done a trial with a larger sample size rather than longer duration. |
| **Key issue 2:** Selection of data used to inform the model inputs<br><br>1) Do you have any general comments on this issue?<br><br>2) How do you expect the baseline attack rates to compare between berotralstat and SoC?<br><br>3) In the presence of substantial degree of uncertainty due to small sample size, do you expect the attack rates and attack rate reductions in the ITT population to be similar and thus generalisable to the proposed positioning subgroup? | This is again a difficulty when dealing with very small sample sizes.<br><br>Not sure I fully understand this question, but given that participants were randomized to both groups, I would expect baseline rates to be the same in both treatment groups.<br><br>Difficult to be absolutely certain about this. I would not expect prior treatment with androgens themselves to make a difference with a sufficient washout period. However, patients previously treated with androgens may not be the same as patients not treated with androgens, as there may have been reasons e.g. more severe disease that resulted in them taking androgens in the first place. |

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| 4) In your opinion, what impact does prior androgen use have on attack rates? Do you consider androgen use at baseline would modify the relative response to berotralstat? | Please see above. |
| 5) Would you expect the percentage reduction in attack rates in patients with no prior androgen use to be similar and thus generalisable to those patients with prior androgen use? | Please see above as well. This question is important to consider as there is a current supply shortage of androgens, and in the future, patients may not have the option of having androgen therapy if the supply issue is not resolved. |
| **Key issue 3:** Extrapolation of attack rates beyond the follow-up period of the trial | |
| 1) Do you have any general comments on this issue? | No |
| 2) In the berotralstat arm, would you expect percentage reduction in attacks for responders beyond 3 months more appropriate using average baseline | If looking purely at response to berotralstat where it is continued, it would seem to me that using the baseline rate for responders would be better as this removes any potential variation introduced by non-responders. The small sample size does make this an issue though. |

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| attack rate of the wider group at the start of the trial or baseline attack rate of responders only? | |
| 3) For berotralstat, do you expect that the efficacy in terms of percentage reductions in acute attacks increases further with longer follow-up beyond month 3? | Given the kinetics of berotralstat, it is unlikely that there will be a lot more change after 3 months of follow-up. |
| 4) In your opinion, what factors are the likely cause of the reduction in attack rates in the SoC arm from months 1 to 5 of the Apex-2 trial? Is this likely associated with placebo effect or natural variation? | Suspect this is most likely due to a combination of factors. There will be some placebo effect, but also potentially natural variation and some regression to mean. It is difficult to work out how much can be attributed to each. Additionally, the magnitude of change in the SoC would not be considered very clinically significant in standard practice. |
| 5) In your opinion, is it appropriate to carry forward the baseline attack rate for the remainder of the model time horizon for the SoC arm? | This would be reasonable to do – although attack frequency can vary, for an individual patient is does tend to be relatively consistent when averaged out over time. |

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| 6) In your opinion, do you expect the individual attack frequency to be similar or vary from month to month in either of the berotralstat or SoC arms? | In general, I would expect attack frequency to be relatively consistent from month to month in both arms. There will be some variability as Individual patients may have more or fewer attacks due to external factors e.g. stress, although over a longer period of time, things tend to average out. |
| **Key issue 4:** Characterizing uncertainty around the ICER (PSA)<br><br>1) Do you have any general comments on this issue? | This is again an issue with small sizes in the trial. |
| **Key issue 5:** The use of utility values from a published study in preference to EQ-5D data collected in the APeX-2 trial<br><br>1) Do you have any general comments on this issue?<br><br>2) In your opinion, what is the impact on patients experiencing an attack in the proposed positioning subgroup | EQ-5D may not be the most appropriate measure to assess QoL in HAE. |

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| compared to the rest of the patient population in the trial? i.e. no prior androgens and/or fewer than 2 attacks per month. Is the impact on the wider population generalisable to the proposed positioning subgroup? | I would the impact of attacks in both groups (assuming the attacks are of the same severity) to have the same level of impact. |
| 3) During attack free periods, how would you expect quality of life to compare between people having berotralstat compared with those having SoC? | I would expect QoL in people with beotralstat to be better compared to those on SoC in attack free periods, as there is less anxiety/worry about the next attack if overall attack frequency is reduced. |
| 4) How would you expect the severity, location and frequency of attacks to impact a person's quality of life? Do you consider the impact is likely to be similar for all attacks, or to vary for each different attack, based on severity, location and frequency of the attack? | I would expect the impact to vary depending on severity, location and frequency of attacks. Clearly more severe, more frequent attacks would have a greater impact. However, even moderate attacks may have a significant impact e.g. hand swelling resulting in the inability to perform daily functions is very significant even though it is not life threatening. |

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| **Key issue 6:** The inclusion of carer disutility in the base case analysis | |
| 1) Do you have any general comments on this issue? | I think HAE attacks do result in carer disutility – the main issue is working out how much disutility there is. |
| 2) What is the caregiver burden of acute HAE attacks? How does this impact their quality of life as carers? | As HAE attacks are disabling, this does result in carers having to either care for the patient or take over responsibilities that the patient would have to do (e.g. cooking or picking up children from school etc). Quality of life is also affected beyond just what needs to be done to care for the patient as the attacks can be very unpredictable, so it is not clear when a carer may have to provide care. |
| 3) Is it appropriate to expect impact on carers to be same for every attack, including cases where a patient does not require any treatment for an acute attack? Or would the impact on carers vary dependent on the severity, frequency and location of the acute attack? | The impact on carer is likely to vary depending on multiple factors. Severe attacks would have the greatest impact but even moderate/milder attacks may have impact if untreated e.g. someone with swelling affecting both hands may be unable to many activities of daily living and require help for that. |
| 4) Do you consider the inclusion of carer disutility for patients experiencing acute attacks appropriate for this appraisal? | Yes, inclusion of carer disutility would be appropriate. The main question would be the magnitude of this. |

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| 5) The magnitude of carer disutility in the company submission seems large when compared to the range identified in the previous NICE TAs (0.01 to 0.173 per year), the majority of which include MS, Alzheimer's and paediatric treatments. How do you think the carer disutility for HAE acute attacks compares with the disease areas mentioned? | Difficult for me to comment on this as I am not so familiar with the data in MS or Alzheimers or paediatric treatments. Did the studies looking at MS and Alzheimers take the most severe patients or was this spread or with different levels of severity? If ones takes only the patients with severe Alzheimers/MS, then yes I would expect carer disutility to be higher in that scenario compared to the average HAE patient. I am not sure how it compares if one is looking at the whole spread of Alzheimers or MS though. |
| **Key issue 7:** The attack costs applied in each arm<br><br>1) Do you have any general comments on this issue?<br><br>2) For the treatment of acute attacks, how would you expect the costs associated with berotralstat to compare with SoC? | In general, I would expect prophylactic treatment to reduce both the frequency and severity of HAE attacks. This should result in lower costs per attack overall. It would be helpful if the company could confirm that berotralstat does reduce attack severity from their data.<br><br>If berotralstat does reduce attack severity, I would expect this to impact on treatment cost per attack. |

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| 3) How often does the treatment of acute attacks require multiple administrations? How would you expect multiple administrations for treatment of acute attacks to compare between berotralstat and SoC? | It is reported that about 10% of people who treat their attacks using icatibant (which would be the most commonly used treatment for acute attacks) need a second dose. If berotralstat does reduce attack severity, I would expect the number of people who require a second dose of treatment to reduce. |
| 4) For the management of acute attacks, how would you expect the resource use costs associated with berotralstat to compare with SoC? | Sorry, I am not completely clear about what is meant by resource use in the question. If this refers to use of healthcare resources e.g. A&E visits, then again I would expect costs to be lower with berotralstat compared to SoC as attacks are less severe. This is likely to be a smaller number of people though as many people with HAE tend to self-manage their attacks at home or with their carers. |
| Are there any important issues that have been missed in ERG report? | |

**PART 3 -Key messages**

16. In up to 5 sentences, please summarise the key messages of your statement:

- Berotralstat is currently the only custom designed oral preventative/prophylactic medication for people with HAE
- There is a significant unmet need for people with HAE who do not qualify for prophylaxis under the NHSE criteria but who still have very significant disease

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Thank you for your time.

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

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**Your privacy**

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

## Clinical expert statement & technical engagement response form

# Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

**Information on completing this form:**

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Wednesday 21 April 2021**.

**Completing this form**

**Part 1** can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

**Important information on completing this expert statement**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

| **PART 1 – Treating a patient with acute attacks of hereditary angioedema and current treatment options** | |
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| **About you** | |
| 1. Your name | **Tomaz Pereira Garcez** |
| 2. Name of organisation | **Manchester University NHS Foundation Trust (also representing British Society of Allergy and Clinical Immunology)** |
| 3. Job title or position | **Consultant Immunology (Chair of BSACI Clinical Immunology Committee)** |
| 4. Are you (please tick all that apply): | ☒ an employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ a specialist in the treatment of people with acute attacks of hereditary angioedema?<br>☒ a specialist in the clinical evidence base for acute attacks of hereditary angioedema or technology?<br>☐ other (please specify): |
| 5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☐ yes, I agree with it<br>☐ no, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☒ other (they didn't submit one, I don't know if they submitted one etc.) |

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| 6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.) | ☐ yes |
| 7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **N/A** |
| **The aim of treatment for acute attacks of hereditary angioedema** | |
| 8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.) | To stop attacks and allow resumption of normal activities; stopping attacks limits pain and can avoid fatalities (laryngeal swellings are associated with risk of death)<br>For prevention the aim is to reduce the frequency and severity of attacks; we should aim where possible to allow patients to live a "normal" life without constant fear of severe attacks |
| 9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, | For acute attacks termination of the attack and resolution of symptoms; stopping progression; allowing resumption of normal activities<br>For prevention reduction in impact of disease / able to function normally for more time proportionally |

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| or a reduction in disease activity by a certain amount.) | |
| 10. In your view, is there an unmet need for patients and healthcare professionals in acute attacks of hereditary angioedema? | The lack of effective oral acute treatment is an unmet need as all effective acute treatment is parenteral; the other unmet need is educational as awareness of this disease is lacking in general medical fields<br>In prophylaxis similarly there is a lack of available effective preventative therapy; currently only those with the most severe disease have access to effective parenteral prophylaxis and those with lower frequency disease would only have the option of attenuated androgens, which although effective are currently in limited supply and have significant tolerance issues for a number of patients |
| **What is the expected place of the technology in current practice?** | |
| 11. How is the condition currently treated in the NHS? | The technology is placed for preventative therapy for patients with frequent swellings / attacks |
| • Are any clinical guidelines used in the treatment of the condition, and if so, which? | There are international, national and NICE / NHS England policy documents on the management of HAE. |
| • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) | The pathway differs across the NHS and clinical teams; but is broadly similar and includes involving patients in the discussion on options applicable to them. Clinical teams generally encourage patients to be involved in their treatment decisions and help to guide them towards self treatment options. Having an additional oral prophylactic option to present to patients with have a significant impact on the current options and allow patients the ability to achieve better disease control. |

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| • What impact would the technology have on the current pathway of care? | |
| 12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? | The technology will likely be used / offered to patients that are currently offered attenuated androgens (where these patients either have contraindications to attenuated androgens, have been intolerant of androgens or where androgens are not available). The technology could be offered as an alternative to androgens presenting a different efficacy and safety profile. The technology could also be considered in patients who are eligible for parenteral prophylaxis therapy as an alternative (either due to preference or intolerance / difficulties with parenteral therapy) |
| • How does healthcare resource use differ between the technology and current care? | Oral therapy, different side effect profile |
| • In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.) | Specialist clinics to initiate and monitor |
| • What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.) | Minimal training of staff required – but this is for staff already experienced in the condition |
| 13. Do you expect the technology to provide clinically meaningful | Yes – providing an alternative preventative therapy will enable patients to improve disease control |

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| benefits compared with current care? | |
| • Do you expect the technology to increase length of life more than current care? | Although this is possible, with access to acute therapy fatalities due to HAE are uncommon; the impacts on length of life might be achievable secondary to improved quality of life, reduced disease burden and related benefits |
| • Do you expect the technology to increase health-related quality of life more than current care? | Yes – current options are very limited and there is an unmet need for preventative therapy in the group of patients with problematic disease not meeting the criteria for parenteral effective prophylaxis. Prophylaxis will reduce burden of disease and improve quality of life and productivity, not only for the patient, but also for any carers |
| 14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? | Traditionally attenuated androgens have not been favoured by younger female patients due to virilising effects. The technology would offer an alternative therapy for this group of patients particularly. The other groupd would include any with needle phobia and therefore not ideal for parenteral therapy. |
| **The use of the technology** | |
| 15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant | Easier for patients to use as the treatment is oral; therefore also easier for professional teams to prescribe / advise on<br><br>There are contraindicated medications and interactions with some other medications; particularly relevant is oral contraception |

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| treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.) | |
| 16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing? | Start will be based on patient preferences if meeting criteria (?attack frequency) and stopped if not tolerated or ineffective |
| 17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? | The technology will help to control and reduce the frequency and severity of episodes of swelling, leading to less use of rescue medication and also less reliance on health care and carers. This would have a psychological benefit not only on the patient but also carers |
| 18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it | Yes and oral preventative therapy that is generally tolerated, where there is currently a gap in therapy. This is particularly beneficial for those with limited ability to self treat with injections or where there are contraindications to other therapies (or other therapies are not available – such as attenuated androgen, which are in short supply globally) |

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| improve the way that current need is met? | |
| • Is the technology a 'step-change' in the management of the condition? | Yes – a novel agent and use of the oral route for preventative therapy |
| • Does the use of the technology address any particular unmet need of the patient population? | Yes provides effective prophylaxis to a group currently without any preventative therapy |
| 19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life? | The main S/E is self limiting gastrointestinal effects; this is unlikely to have a significant impact on the benefits of the technology. Drug interactions with progesterone only oral contraception could present a limitation of use in some patients |
| **Sources of evidence** | |
| 20. Do the clinical trials on the technology reflect current UK clinical practice? | Broadly yes – in the UK attenuated androgen are used more frequently in this condition than in some other countries |
| • If not, how could the results be extrapolated to the UK setting? | |

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| • What, in your view, are the most important outcomes, and were they measured in the trials? | Reduction in frequency and severity of swelling episodes; yes measured |
| • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? | |
| • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | None I am aware of |
| 21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence? | No |
| 22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA606]? | There have been multiple new publications on the comparator therapy, including some real world data publications |

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| 23. How do data on real-world experience compare with the trial data? | For this technology I am not aware of published real world data |
| **Equality** | |
| 24a. Are there any potential equality issues that should be taken into account when considering this treatment? | Not in my opinion |
| 24b. Consider whether these issues are different from issues with current care and why. | |

| PART 2 – Technical engagement questions for clinical experts | |
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| **Issues arising from technical engagement** | |
| We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.<br>The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.<br>For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee. | |
| **Key issue 1:** Limited evidence base<br><br>1) Do you have any general comments on this issue? | Rare condition with difficulty getting larger numbers in studies |
| 2) Provided the small sample size of the trial and the company's proposed positioning, do you consider the evidence from the trial to be representative of HAE in UK clinical practice? | Evidence is representative in my view; there may be patients that have not tried attenuated androgens that would also benefit, including those unable to get androgens due to global shortages |

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| 3) Is 24 months follow-up appropriate to capture key outcomes and inform key clinical effectiveness parameters? | 24 months follow up would capture outcomes and longer follow up unlikely to be of benefit for efficacy |
| **Key issue 2:** Selection of data used to inform the model inputs<br><br>1) Do you have any general comments on this issue?<br><br>2) How do you expect the baseline attack rates to compare between berotralstat and SoC?<br><br>3) In the presence of substantial degree of uncertainty due to small sample size, do you expect the attack rates and attack rate reductions in the ITT population to be similar and thus generalisable to the proposed positioning subgroup? | With low numbers of patients in a rare disease that is variable it is difficult to answer the questions posed. Baseline attack rates can vary simply due to the disease pattern and sample size. We have to consider the data provided, and accept that changes in attack rates will be variable between individuals with this rare condition. The reasons for one sub group to have a different response to others (based on prior use of androgens for example) is likely related to the small sample size and variability of this disease. |

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| 4) In your opinion, what impact does prior androgen use have on attack rates? Do you consider androgen use at baseline would modify the relative response to berotralstat?<br><br>5) Would you expect the percentage reduction in attack rates in patients with no prior androgen use to be similar and thus generalisable to those patients with prior androgen use? | |
| **Key issue 3:** Extrapolation of attack rates beyond the follow-up period of the trial<br><br>1) Do you have any general comments on this issue?<br><br>2) In the berotralstat arm, would you expect percentage reduction in attacks for responders beyond 3 months more appropriate using average baseline | In assessing response / percentage reduction in attack rate it would appear sensible to use the baseline attack rate for the group of interest only, accepting that the groups may be small |

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| attack rate of the wider group at the start of the trial or baseline attack rate of responders only? | |
| 3) For berotralstat, do you expect that the efficacy in terms of percentage reductions in acute attacks increases further with longer follow-up beyond month 3? | I would not expect or be able to predict additional benefit beyond the benefit achieved at 3 months; the variability of the disease and small sample size make it difficult to comment further |
| 4) In your opinion, what factors are the likely cause of the reduction in attack rates in the SoC arm from months 1 to 5 of the Apex-2 trial? Is this likely associated with placebo effect or natural variation? | The natural variation of this disease and the possibility of placebo effect cannot be confirmed; this condition is however prone to fluctuation based on psychological factors and therefore there could be a placebo effect, followed by a rebound simply due to the expectations of the patient |
| 5) In your opinion, is it appropriate to carry forward the baseline attack rate for the remainder of the model time horizon for the SoC arm? | It would be reasonable to carry forward the baseline attack rate, despite the condition being variable |

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| 6) In your opinion, do you expect the individual attack frequency to be similar or vary from month to month in either of the berotralstat or SoC arms? | Although the condition is variable (often due to intercurrent events / life events) most patients will have stable attack rates over a long time window |
| **Key issue 4:** Characterizing uncertainty around the ICER (PSA)<br><br>1) Do you have any general comments on this issue? | |
| **Key issue 5:** The use of utility values from a published study in preference to EQ-5D data collected in the APeX-2 trial<br><br>1) Do you have any general comments on this issue?<br><br>2) In your opinion, what is the impact on patients experiencing an attack in the proposed positioning subgroup compared to the rest of the patient population in the trial? i.e. no prior | Impact of an attack is unlikely to be different based on prior treatment or frequency of events but more related to personal factors and attack severity |

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| androgens and/or fewer than 2 attacks per month. Is the impact on the wider population generalisable to the proposed positioning subgroup? | |
| 3) During attack free periods, how would you expect quality of life to compare between people having berotralstat compared with those having SoC? | I would expect individuals on effective preventative therapy to experience better QoL that those not on effective preventative therapy – this is mainly related to the fear of attacks occurring which would be greater if not on preventative therapy (assuming all other characteristic similar at baseline) |
| 4) How would you expect the severity, location and frequency of attacks to impact a person's quality of life? Do you consider the impact is likely to be similar for all attacks, or to vary for each different attack, based on severity, location and frequency of the attack? | Vary based on severity and risk of harm. All factors are likely to play a part on QoL impact. For example a patient with frequent laryngeal swellings is likely to experience more QoL impact than a patient with infrequent non-dominant hand digit swellings |
| **Key issue 6:** The inclusion of carer disutility in the base case analysis | |

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| 1) Do you have any general comments on this issue? | |
| 2) What is the caregiver burden of acute HAE attacks? How does this impact their quality of life as carers? | Variable depending on the patient and their ability to self manage. Even for the most independent patient however there are likely to be caregiver impacts including support for dependants during an attack. With less independent patients the impact is far greater. This is difficult to quantify |
| 3) Is it appropriate to expect impact on carers to be same for every attack, including cases where a patient does not require any treatment for an acute attack? Or would the impact on carers vary dependent on the severity, frequency and location of the acute attack? | The impact would vary as mentioned above and also based on the severity and incapacitation related to the attack. |
| 4) Do you consider the inclusion of carer disutility for patients experiencing acute attacks appropriate for this appraisal? | Yes |
| 5) The magnitude of carer disutility in the company submission seems large | The comparator diseases mentioned have a more predictable course generally and therefore carer impact, although significant, is able to be planned (to a degree). That is not the case in HAE as the swellings are less predictable in when they might occur. This is |

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| when compared to the range identified in the previous NICE TAs (0.01 to 0.173 per year), the majority of which include MS, Alzheimer's and paediatric treatments. How do you think the carer disutility for HAE acute attacks compares with the disease areas mentioned? | likely to increase the carer impact. Quantification of carer impact will not be easy, but it is reasonable to include it |
| **Key issue 7:** The attack costs applied in each arm<br><br>1) Do you have any general comments on this issue?<br><br>2) For the treatment of acute attacks, how would you expect the costs associated with berotralstat to compare with SoC?<br><br>3) How often does the treatment of acute attacks require multiple administrations? How would you expect | <br><br><br><br>This would be related to severity – it is likely that severity and frequency would be reduced by effective preventative therapy, making it less costly to manage acute attacks when on preventative therapy.<br><br>Around / less than 10% of attacks likely to need repeat treatment. This is likely to be lower when effective preventative therapy is in place |

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| multiple administrations for treatment of acute attacks to compare between berotralstat and SoC?<br><br>4) For the management of acute attacks, how would you expect the resource use costs associated with berotralstat to compare with SoC? | Should be lower based on the assumptions above; less severe attacks would generally require less resource cost to manage |
| Are there any important issues that have been missed in ERG report? | |

**PART 3 -Key messages**

16. In up to 5 sentences, please summarise the key messages of your statement:

- This technology has the potential to have a significant benefit to patient care in a rare disease with very limited treatment options
- Controlling and reducing severity and frequency of attacks in HAE will have benefits on the overall care of patients with HAE and their carers
- There is a clear need for additional treatment options that are easy to take for HAE (oral for example) like this technology and it would be a real disadvantage to our patients if we were unable to provide this technology as an option
-
-

Thank you for your time.

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

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**Your privacy**

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

## Patient expert statement and technical engagement response form

# Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

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

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

**About this Form**
In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Wednesday 21 April 2021**.

**Completing this form**

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

**Important information on completing this expert statement**

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

| PART 1 – Living with or caring for a patient with acute attacks of hereditary angioedema and current treatment options | |
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| **About you** | |
| 1.Your name | **Laura Szutowicz** |
| 2. Are you (please tick all that apply): | ☐ a patient with acute attacks of hereditary angioedema?<br>☐ a patient with experience of the treatment being evaluated?<br>☐ a carer of a patient with acute attacks of hereditary angioedema?<br>☒ a patient organisation employee or volunteer?<br>☐ other (please specify): |
| 3. Name of your nominating organisation. | HAE UK PATIENT SUPPORT AND ADVOCACY CHARITY |
| 4. Has your nominating organisation provided a submission? Please tick all options that apply. | ☐ No, (please review all the questions below and provide answers where possible)<br>☒ Yes, my nominating organisation has provided a submission<br>☐ I agree with it and **do not wish to** complete a patient expert statement<br>☒ Yes, I authored / was a contributor to my nominating organisations submission<br>☐ I agree with it and **do not wish to** complete this statement<br>☒ I agree with it and **will be** completing |

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| 5. How did you gather the information included in your statement? (please tick all that apply) | ☒ I am drawing from personal experience.<br>☒ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: Member/Patient comments, Member/Patient surveys, consultations, 'thinktank' groups etc, monitoring our social media accounts, attending clinics etc (in days when Covid 19 was not an issue!)<br>☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference<br>☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference<br>☐ I have not completed part 2 of the statement |
| **Living with the condition** | |
| 6. What is your experience of living with acute attacks of hereditary angioedema?<br><br>If you are a carer (for someone with acute attacks of hereditary angioedema) please share your experience of caring for them. | Patient remarks are highlighted in purple<br><br>Hereditary Angioedema is characterised by unpredictable and sporadic attacks of subcutaneous swelling which can attack anywhere and varies from mild to lifethreatening if it affects airways. Historically, it is considered that over 30% of people affected by HAE died from airway obstruction. It is still a major concern to patients. In the past four years at least two patients in UK have died this way.<br>There are no particular triggers for these attacks, as in allergic conditions, but some common triggers emerge, notably hormonal changes, stress and anxiety (eg exams or even 'happy stress ' like family events) invasive procedures such as dentistry, minor surgery, infections such as colds, flue, tooth decay. Sometimes repetitive actions such as painting, even walking can trigger attacks.<br>Patients therefore live in constant fear of having an attack.. |

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| | Attacks can occur in peripheries such as feet, hands and limbs, abdominally, genitally, facially and elsewhere. Swellings reach a very large size in a short time - circa 30-40 minutes - and then take 2 or more days to resolve. Available treatments will stop swelling but will not help it to resolve. HAE swelllings are unresponsive to antihistamines or steroids. It is not unusual for swellings to occur in more than one location in an attack.<br><br>Swellings are painful 'I feel I want to take a knife and cut into them to relieve them'<br><br>At present patients suffering frequent attacks (more than two a week) are allowed to use C1-INH (iv infusions) or lanadelumab (subcutaneous) as prophylaxis. Most have fewer attacks and treat on demand with C1-INH iv infusions as replacement therapy) and/or Icatibant (a bradykinin receptor antagonist). Some patients respond well to oral attenuated androgens, but these are increasingly difficult to obtain.<br><br>Attacks in peripheries such as feet can render the patient unable to wear shoes or to walk. In hands, they cannot use simple equipment for cooking, writing or driving. Abdominal attacks are so painful that they have often been confused with appendicitis or other abdominal conditions and so patients have has unnecessary surgery. The swelling is such that it gives the appearance of late-stage pregnancy and patients find wearing clothing difficult because of waistbands etc.<br><br>Even patients using prophylaxis treatment will have breakthrough attacks although they are often considerably reduced in severity<br><br>Patients relate constantly planning their lives around the condition, 'It's always at the back of my mind that I might have an attack' 'we used to plan family parties or get-togethers and yet never be able to get there' 'my daughter has had to live with the fact that she cannot go on school trips because I may not be able to get there to give her treatment'<br><br>Children can suffer from severe limitation to school life and education, although they tend to not develop severe condition until puberty, so often it is later school life and further education that suffers.<br><br>'Throughout my childhood, I had numerous swellings to the face, hands and feet but when I was taken to the GP's they all brushed it off as an allergic reaction but never tested me for anything. I learnt to live with the swellings even though they were painful and |

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| | embarrassing as people would stare and other children would tease. When I was 21, I was taken into hospital with excruciating abdominal pain. Doctors told me it was appendicitis and so I had my appendix removed and spent over a week in the hospital recovering as I developed an infection.'<br><br>Patients are therefore unable to carry out normal day to day tasks and it can affect their work or school lives very badly. As stated previously, there are no discernable triggers as with an allergic condition, but patients are severely affected by stressful situations or infections such as colds, flu, infected teeth etc. There is considerable psychological damage caused by the constant anxiety and socio-economic consequences caused by lowered educational levels or time absent from work.<br><br>Many patients relate a history of family members dying prematurely due to laryngeal swelling/compromised airways and it is always in their mind that this could happen to them. Parents with an affected child are particularly conscious of this as they fear the child will not inform them of an attack soon enough. 'Mum was very sick all of her life and passed away in 1969 at the age of 24. Her death was caused by a swelling in her throat, unfortunately medical attention came too late.'<br><br>'My grandfather had HAE severely over many years and he died from a throat swelling at the age of 39' |
| **Current treatment of the condition in the NHS** | |
| 7a. What do you think of the current treatments and care available for acute attacks of hereditary angioedema on the NHS? | The present acute treatments available are replacement C1-INH either plasma derived or recombinant product. Which is effective when infused quickly but sometimes patients have to report to A&E if they are unable to carry out their own IV and often they have a struggle to be appropriately treated even though they may carry letters from their immunology team. Other acute treatment is subcutaneous Icatibant which is effective if used early in an attack, but has a short half life and so patients frequently require to use further syringes to prevent further swelling.<br><br>C1-INH can be used as prophylaxis by iv infusion twice per week, or there is also twice monthly subcutaneous injections of lanadelumab which is approved for prophylaxis. |

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| 7b. How do your views on these current treatments compare to those of other people that you may be aware of? | I am not able to comment other than to remark that prophylaxis and prevention of attacks should be preferable to treating attacks when they happen, when swelling can happen so quickly and unexpectedly. |
| 8. If there are disadvantages for patients of **current NHS treatments** for acute attacks of hereditary angioedema (for example how the treatment is given or taken, side effects of treatment etc) please describe these | All forms of acute treatment currently are injectable only. Similarly, prophylaxis is IV infusions of C1-INH twice weekly or twice monthly subcutaneous injections of lanadelumab. Both regimens have some record of breakthrough attacks and IV requires training for patients to self administer. There is also a requirement for giving sets etc, and a relatively sterile situation<br><br>There are some patients who are well managed on oral attenuated androgens, but these require annual liver scans. Many patients are intolerant to these products and report weight gain and mode swings. Attenuated androgens are not licenced to treat HAE |
| **Advantages of this treatment** | |
| 9a. If there are advantages of berotralstat over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others?<br><br>9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? | Berotralstat is the first licensed oral product to provide prophylaxis against attacks of HAE<br><br>It provides effective prevention of attacks in an easy to administer once daily oral regimen which is a great advantage over present injectables<br><br>‘ started berotralstat about 6 weeks ago, only one attack since and that was in the first week I started taking it. Down from 1-2 a week. Woohoo!’<br><br>As recorded above, HAE considerably impacts on patients’ life and life chances. Therefore an easy to administer prophylactic treatment will be a great advantage to patients.<br><br>Good control of attacks, permits patients to plan and carry out their plans. Also reduces anxiety and will improve mental health. Anxiety has been shown to be a trigger for HAE attacks. |

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| 9c. Does berotralstat help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these. | Easy to administer, requires no training and provides effective control (or reduction of severity/frequency of attacks) |
| **Disadvantages of this treatment** | |
| 10. If there are disadvantages of berotralstat over current treatments on the NHS please describe these? For example, are there any risks with berotralstat? If you are concerned about any potential side affects you have heard about, please describe them and explain why. | I have not heard of any side effects but would make the point that HAE is notoriously variable and so what suits one patient may not suit another. |
| **Patient population** | |
| 11. Are there any groups of patients who might benefit more from berotralstat or any who may benefit less? If so, please describe them and explain why.<br><br>Consider, for example, if patients also have other health conditions (for example difficulties with | There is a significant group of patients who do not fall into the current criteria for prophylaxis and yet are significantly disabled by their HAE and spend many days per week suffering from an attack. They tend to treat ad-hoc with C1 or icatibant. However, prevention of attacks must be preferable to allowing attacks to start, as there is always risk involved with such an approach. These patients would be suitable for berotralstat, as will patients who have been on attenuated androgens and so are used to an oral regimen. There are also patients who are not able to carry out their own venepuncture or injections for whatever reasons and have to rely on a family member, spouse or similar to treat them. The ease of use of this product will relieve them of this burden |

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| mobility, dexterity or cognitive impairments) that affect the suitability of different treatments | An oral treatment such as this is considerably easier to carry for holidays etc as it requires no special storage conditions, nor ancillary equipment..<br>Finally, it is another treatment which some patients and clinicians will find suits them, patient choice is very important to good management of HAE. |
| **Equality** | |
| 12. Are there any potential equality issues that should be taken into account when considering acute attacks of hereditary angioedema and berotralstat? Please explain if you think any groups of people with this condition are particularly disadvantaged.<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics<br><br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme | I do not think there are any equality issues, although some GPs are reluctant to relinquish control over androgen patients who have been historically treated as a shared care arrangement. This could potentially create an inequality in that these patients may no be able to access the most modern technologies. |

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| More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights. | |
| **Other issues** | |
| 13. Are there any other issues that you would like the committee to consider? | I would suggest that reduction in severity/duration of attacks should also be taken into account rather than the absolute of absence of attacks as a measure of effectiveness. Attacks where severity is greatly reduced are often tolerated without further treatment. |

**PART 2 – Technical engagement questions for patient experts**

**Issues arising from technical engagement**

We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.

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| 14a. Are the comparators (the current treatment available in the NHS) in the company submission used in the NHS for treating the condition? | There is not really a direct comparator; the present treatments are injectables. The only possible oral comparator is not licenced for HAE treatment and has considerable sideeffects including a requirement for annual liver scans. |
| 14b. Is the assessment tool used in the clinical trial appropriate for assessing the severity of this condition? | I am not qualified to judge this. |
| 14c. What are the main benefits of this treatment for patients? If there are several benefits please list them in order of importance. Are there any benefits of this treatment that have not been captured?<br><br>d. What are the benefits of this treatment for carers? | Easy administration being an oral tablet<br>Simple regimen; once daily<br>No need for specialist training<br>Good control of symptoms<br>Another choice for patients/clinicians<br>Easy storage of medication<br><br>No need for infusion buddy or for member of family to be trained in venepuncture. No need for carer to be available 24/7 for ad-hoc treatments |
| **Key issue 1:** Limited evidence base | This is not unusual in conditions such as HAE which is very rare; incidence circa 1;50,000 |

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| • Do you have any general comments on this issue? | |
| **Key issue 2:** Selection of data used to inform the model inputs<br><br>• Do you have any general comments on this issue? | I am not qualified to comment |
| **Key issue 3:** Extrapolation of attack rates beyond the follow-up period of the trial<br><br>• Do you have any general comments on this issue? | I am not qualified to comment |
| **Key issue 4:** Characterizing uncertainty around the ICER (PSA)<br><br>• Do you have any general comments on this issue? | I am not qualified to comment |

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| **Key issue 5:** The use of utility values from a published study in preference to EQ-5D data collected in the APeX-2 trial<br><br>• Do you have any general comments on this issue? | I am not qualified to comment<br><br>None |
| **Key issue 6:** The inclusion of carer disutility in the base case analysis<br><br>• Do you have any general comments on this issue? | This impact of a condition such as HAE on carers is often underestimated. The carer will often suffer the same anxiety as the patient, in some cases exacerbated for example when a parent is also the carer and feels responsible for having 'passed on' the condition. There are many instances where a carer (typically female) has given up their career in order to be available in case of the patient having an attack. |
| **Key issue 7:** The attack costs applied in each arm<br><br>• Do you have any general comments on this issue? | None |
| 15. Are there any important issues that have been missed in ERG report? | |

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**PART 3 -Key messages**

16. In up to 5 sentences, please summarise the key messages of your statement:

- This is an oral treatment developed specifically to treat HAE and licenced as prophylaxis, currently there is no licenced oral prophylactic treatment
- It has good implications for treatment of patients who fall outwith the present criteria for propyhylaxis and yet are still considerably disabled by their condition
- Simple regimen of once a day oral tablet reduces burden of management of HAE for patients and carers
- Good control of attacks has been established
- Important to assess not just numerical reduction in number of attacks, but also to value reduction in severity and duration

Thank you for your time.

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

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**Your privacy**

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☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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NICE National Institute for Health and Care Excellence

## Patient expert statement and technical engagement response form

# Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

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

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**About this Form**

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In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

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Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

| PART 1 – Living with or caring for a patient with acute attacks of hereditary angioedema and current treatment options | |
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| **About you** | |
| 1.Your name | **Rachel Annals** |
| 2. Are you (please tick all that apply): | ☐/ a patient with acute attacks of hereditary angioedema?<br>☐ a patient with experience of the treatment being evaluated?<br>☐ a carer of a patient with acute attacks of hereditary angioedema?<br>☐/ a patient organisation employee or volunteer?<br>☐ other (please specify): |
| 3. Name of your nominating organisation. | HAE UK |
| 4. Has your nominating organisation provided a submission? Please tick all options that apply. | ☐ No, (please review all the questions below and provide answers where possible)<br>☐ / Yes, my nominating organisation has provided a submission<br>☐ I agree with it and **do not wish to** complete a patient expert statement<br>☐ Yes, I authored / was a contributor to my nominating organisations submission<br>☐ I agree with it and **do not wish to** complete this statement<br>☐ I agree with it and **will be** completing |

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| 5. How did you gather the information included in your statement? (please tick all that apply) | ☐/ I am drawing from personal experience.<br>☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience:<br>☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference<br>☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference<br>☐ I have not completed part 2 of the statement |
| **Living with the condition** | |
| 6. What is your experience of living with acute attacks of hereditary angioedema?<br><br>If you are a carer (for someone with acute attacks of hereditary angioedema) please share your experience of caring for them. | I have experienced attacks of HAE since around the age of 2 years old. I suffered one or two severe abdominal attacks a fortnight up until I was diagnosed at the age of 15. Having such frequent attacks meant I missed a lot of school and I struggled with friendships, often missing a lot of social events and group activities.<br>Before my diagnosis, my parents took me to see many different consultants and specialist doctors to try and find out what was causing my frequent stomach attacks and random swellings. I tried many different diets, eliminating different foods because the doctors could only assume I had a severe allergy to something, but no one could never work out what exactly this was.<br>Finally, at the age of 15, I saw another new doctor. This doctor mentioned HAE and, although he was unsure that I had this because it was so rare, he decided to run some blood tests for it, and I finally had my diagnosis. Because of its hereditary nature, other members of my family were tested, and we discovered my sister, brother, father and grandmother were also found to have HAE, although they were largely symptom free at that time. We believe my great grandmother, who had passed away not long before my diagnosis, also had HAE because she used to |

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| | suffer severe facial swellings, but she was always told these swellings were an allergic reaction to something unknown. Thankfully these swellings never spread to her larynx.<br><br>After my diagnosis, I was prescribed androgens and they worked so well that it enabled me to live a normal life, passing my exams, attending college and securing a full-time job. I did have breakthrough attacks every few months, but this was still such a huge improvement, and I felt normal.<br><br>After 17 years taking androgens, and in consultation with my HAE consultant, I stopped taking them to start a family. My consultant had arranged to have C1 inhibitor available for treatment of acute attacks. Whilst this treatment was good, the inconvenience it caused by having to have it administered in hospital was huge and it started to impact on my work and social life; I was worried about travelling too far from my local hospital for fear of having an attack and not being able to get back quick enough for treatment. This caused me to become quite anxious and I would regularly cancel social activities for fear of having an attack and being unable to get home. My attacks are mostly abdominal and can come on extremely quickly, sometimes as quick as 10 minutes.<br><br>In 2014, after appeals, I was finally accepted to self-administer my C1 at home, and this was a huge turning point for me.<br><br>My attacks now happen approximately every four days, but having the medication close to hand and being able to self-administer means I can carry on my life as normal. It can be a little inconvenient having to carry medication with me in case of an attack and having to take time out or cancel arrangements at the last minute to enable me to find a quiet place to self-administer, but it starts to work within 30 minutes and I can then continue as normal.<br><br>Having HAE can cause many difficulties and inconveniences, but I do not let it stop me from enjoying my life, playing sports, managing a busy family and travelling all over the world (pre-covid). |

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| **Current treatment of the condition in the NHS** | |
| 7a. What do you think of the current treatments and care available for acute attacks of hereditary angioedema on the NHS?<br><br>7b. How do your views on these current treatments compare to those of other people that you may be aware of? | There are many different treatments available for patients with HAE but some of these are restricted to patients who suffer a particular number of attacks per week. Some of the treatments, particularly androgens, cause side effects in many people so make them unsuitable. The care for patients varies around the country and not all patients are aware of the different treatment options that may be available to them.<br><br>Patients find it frustrating that they may not have access to all HAE treatments because they do not necessarily fit the criteria. Their attacks can vary and often be extremely severe, but not frequent enough to be allowed certain treatments, thus limiting their quality of life. |
| 8. If there are disadvantages for patients of **current NHS treatments** for acute attacks of hereditary angioedema (for example how the treatment is given or taken, side effects of treatment etc) please describe these | Many patients are still treated with androgens which, in many, cause a range of side effects. Patients often put up with these side effects because they are better than suffering attacks of HAE. Other patients are needle phobic or have poor veins meaning intravenous medication is not really possible. These patients have to attend A&E departments if suffering a severe attack and will often 'put up with' non severe attacks (which still limits their day-to-day activities) because it is difficult getting treatment in A&E if the attacks is not severe enough. |
| **Advantages of this treatment** | |
| 9a. If there are advantages of berotralstat over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your | Berotralstat would be a great option for patients who cannot use intravenous medication because of needle phobia, poor veins or for religious reasons for example. The treatment being oral is also much easier and quicker to administer and would have far less impact on a patient's day to day life, with the added benefit of being pain free, so would be a positive alternative to the current treatments |

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| ability to continue work, education, self-care, and care for others?<br><br>9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?<br><br>9c. Does berotralstat help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these. | offered.<br>The biggest advantage is the administration route, having an oral preventative medication is a huge step forward in HAE treatment and would appeal to so many HAE patients due to the ease and speed of administration.<br>This would also be a new preventative treatment option for those who intravenous medication isn't possible. |
| **Disadvantages of this treatment** | |
| 10. If there are disadvantages of berotralstat over current treatments on the NHS please describe these? For example, are there any risks with berotralstat? If you are concerned about any potential side affects you have heard about, please describe them and explain why. | I personally cannot see any disadvantages to this medication. The only disadvantage others might see would be the frequency of treatment and remembering to take it every day. |

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| **Patient population** | |
| 11. Are there any groups of patients who might benefit more from berotralstat or any who may benefit less? If so, please describe them and explain why.<br><br>Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments | All HAE patients could benefit from this medication. For those who are needle phobic, have poor veins or for religious reasons cannot use intravenous medications or needles, this treatment would be of real benefit to them particularly. |
| **Equality** | |
| 12. Are there any potential equality issues that should be taken into account when considering acute attacks of hereditary angioedema and berotralstat? Please explain if you think any groups of people with this condition are particularly disadvantaged.<br><br>Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, | |

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| religion or belief, sex, and sexual orientation or people with any other shared characteristics<br><br>More information on how NICE deals with equalities issues can be found in the NICE equality scheme<br><br>More general information about the Equality Act can and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights. | |
| **Other issues** | |
| 13. Are there any other issues that you would like the committee to consider? | I think it is important to mention the psychological side of living with HAE. Patients, especially those who are severely affected, are often anxious, not knowing when the next attack will arise or how severe it will be. Some patients have had unnecessary operations before diagnosis, leading to anxiety around hospital visits and treatment for HAE. There is still not enough knowledge of HAE in A&E departments and some patients still have difficulties being treated quickly because of this. Having a new, easy to administer medication to prevent attacks of HAE, would really help ease the burden of living with the condition and allow patients, like myself, to live a more normal life without fear of HAE. |

| PART 2 – Technical engagement questions for patient experts | |
|---|---|
| **Issues arising from technical engagement** | |
| We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.<br>The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.<br>For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee. | |
| 14a. Are the comparators (the current treatment available in the NHS) in the company submission used in the NHS for treating the condition?<br><br>14b. Is the assessment tool used in the clinical trial appropriate for assessing the severity of this condition?<br><br>14c. What are the main benefits of this treatment for patients? If there are several benefits please list them in order of | |

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| importance. Are there any benefits of this treatment that have not been captured?<br><br>d. What are the benefits of this treatment for carers? | |
| **Key issue 1:** Limited evidence base<br><br>• Do you have any general comments on this issue? | |
| **Key issue 2:** Selection of data used to inform the model inputs<br><br>• Do you have any general comments on this issue? | |
| **Key issue 3:** Extrapolation of attack rates beyond the follow-up period of the trial<br><br>• Do you have any general comments on this issue? | |

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| **Key issue 4:** Characterizing uncertainty around the ICER (PSA)<br><br>• Do you have any general comments on this issue? | |
| **Key issue 5:** The use of utility values from a published study in preference to EQ-5D data collected in the APeX-2 trial<br><br>• Do you have any general comments on this issue? | |
| **Key issue 6:** The inclusion of carer disutility in the base case analysis<br><br>• Do you have any general comments on this issue? | |
| **Key issue 7:** The attack costs applied in each arm | |

| | |
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| • Do you have any general comments on this issue? | |
| 15. Are there any important issues that have been missed in ERG report? | |
| | |
| **PART 3 -Key messages** | |
| 16. In up to 5 sentences, please summarise the key messages of your statement:<br><br>• I have personal experience of living with HAE from a very young age<br>• I embrace new treatments that will improve the quality of life of HAE patients, like myself and my family members<br>• This new treatment could significantly improve the quality of life of patient living with HAE<br>• This treatment will also lessen the burden on family members of those caring for people with HAE<br>• | |

Thank you for your time.

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

……

**Your privacy**

NICE National Institute for Health and Care Excellence

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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# Technical engagement response form

## Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Wednesday 21 April 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

**Notes on completing this form**

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

**We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

## About you

| | |
|---|---|
| **Your name** | [redacted] |
| **Organisation name – stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank) | **UKPIN** |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **No links to or funding from the tobacco industry.** |

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## Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

| Key issue | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| **Key issue 1:** Limited evidence base | **NO** | **Not aware of any new data on this** |
| **Key issue 2**: Selection of data used to inform the model inputs | **NO** | **It is difficult to be certain whether patients with and without prior experience of androgens would be directly comparable. Assuming a sufficient washout period with androgens, one would not expect a difference between the two groups from the androgens itself. However, patients that were on androgens previously may differ in that they have had more severe disease to start with, which is why they were taking androgens in the first place. I am not sure whether there is any data available to the company that would help work that out though.** |
| **Key issue 3**: Extrapolation of attack rates beyond the follow-up period of the trial | **NO** | The slight decrease in baseline rate in the SoC arm could be due to placebo, natural variation or regression to mean. It is likely that all may contribute to this although it is not possible to exclude a placebo effect. However, the actual magnitude of change in the SoC arm are small and probably not very clinically significant. |
| **Key issue 4:** Characterizing uncertainty around the ICER (PSA) | **YES/NO** | Please provide your response to this key issue, including any new evidence, data or analyses |

| | | |
|---|---|---|
| **Key issue 5:** The use of utility values from a published study in preference to EQ-5D data collected in the APeX-2 trial | NO | There is data from the HELP study of lanadelumab to suggest that EQ-5D-5L is not the most useful measure for assessing QoL in HAE, and that other AE-QOL tool may be a better measure. |
| **Key issue 6:** The inclusion of carer disutility in the base case analysis | **N**O | We would expect from the fact that HAE attacks can be disabling, that there would be carer disutility when a patient suffers from a HAE attack, as patient are left either needing to go to hospital for treatment, or being unable to do activities of daily living and requiring help for this. It would seem sensible to include carer disutility as part of the calculation, although calculating the amount of carer disutility may be less straightforward. |
| **Key issue 7:** The attack costs applied in each arm | **NO** | P**rophylactic treatment would be expected to reduce not just the number of but also the severity of attacks. More severe attacks would usually result in more treatment and potentially multiple doses, whereas with milder attacks, less medication may be used, or a patient may elect not to treat an attack if it is very mild. So, it is clinically plausible that prophylactic treatment could reduce cost spent per attack. Equalising the costs across the treatment arms may result in masking the effect of prophylactic treatment on attack severity, with this benefit not being realized in the analysis.** |

## Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

| Issue from the ERG report | Relevant section(s) and/or page(s) | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|---|
| **Additional issue 1:** Insert additional issue | Please indicate the section(s) of the ERG report that discuss this issue | **YES/NO** | Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making |
| **Additional issue 2:** Insert additional issue | Please indicate the section(s) of the ERG report that discuss this issue | **YES/NO** | Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making |
| **Additional issue N:** Insert additional issue | | | [INSERT / DELETE ROWS AS REQUIRED] |

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## Summary of changes to the company's cost-effectiveness estimate(s)

**Company:** If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

| **Key issue(s) in the ERG report that the change relates to** | **Company's base case before technical engagement** | **Change(s) made in response to technical engagement** | **Impact on the company's base-case ICER** |
|---|---|---|---|
| Insert key issue number and title as described in the ERG report | Briefly describe the company's original preferred assumption or analysis | Briefly describe the change(s) made in response to the ERG report | Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER |
| .. | .. | .. | [INSERT / DELETE ROWS AS REQUIRED] |
| **Company's preferred base case following technical engagement** | **Incremental QALYs: [QQQ]** | **Incremental costs: [£££]** | **Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER** |

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# Technical engagement response form

## Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Wednesday 21 April 2021**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

**Notes on completing this form**

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- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
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- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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## About you

| | |
|---|---|
| **Your name** | [redacted] |
| **Organisation name – stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank) | **Takeda UK Limited** |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | |

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## Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

| Key issue | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|
| **Key issue 1:** Limited evidence base | **NO** | No comment |
| **Key issue 2**: Selection of data used to inform the model inputs | **NO** | No comment |
| **Key issue 3**: Extrapolation of attack rates beyond the follow-up period of the trial | **NO** | No comment |
| **Key issue 4:** Characterizing uncertainty around the ICER (PSA) | **NO** | No comment |
| **Key issue 5:** The use of utility values from a published study in preference to EQ-5D data collected in the APeX-2 trial | **NO** | No comment |
| **Key issue 6:** The inclusion of carer disutility in the base case analysis | **NO** | No comment |

| | | |
|---|---|---|
| **Key issue 7:** The attack costs applied in each arm | **YES** | We agree with the ERG's main comments on this issue. The company, ERG and appraisal committee should be aware of alternative published data sources that may help to inform the acute therapy usage.<br><br>This includes the Longhurst et al. (Allergy Asthma Clin Immunol 2018; 14:28) publication on the Icatibant Outcome Survey in the UK which reports that "C1-INH was used as rescue medication in 12.7% of icatibant-treated attacks (48/378 attacks in 15/57 patients)" in UK patients with HAE.<br><br>Additionally, published data from FAST-1, FAST-2 and FAST-3 clinical trials of icatibant for acute HAE could be considered. Malbrán et al. (Clin Exp Immunol 2014;177:544–553) reports results from the FAST-1 trial for the open-label phase: "A single icatibant injection was used in 300 of the 340 attacks (88.2%)… [two] injections were used in 36 attacks (10.6%) and three injections in four attacks (1.2%)". Baş et al. (Allergy 2013; 68:1452–1459) reports results from the FAST-2 open-label study: "The majority of attacks (89.8%) were successfully treated with a single icatibant injection". Lumry et al. (Int Arch Allergy Immunol 2015;168:44–55) reports results from the FAST-3 clinical trial: Table 2 reports the number of icatibant injections per attack with a range of 0-7.3% of patients requiring 2 or 3 injections across the number of icatibant-treated attacks.<br><br>These published sources may be useful to assess consistency with the current data used in the model and consider in additional scenario analyses. |

## Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

| Issue from the ERG report | Relevant section(s) and/or page(s) | Does this response contain new evidence, data or analyses? | Response |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Additional issue 1:** Excluding adverse event treatment costs from the economic model may introduce a small bias in the model in favour of berotralstat | Section 3.6 (page 36) and Section 4.2.8 (page 64) | **YES** | The ERG noted 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". While this may be the case for costs, the quality of life impact of GI abdominal TEAEs has not been considered or quantified. GI disturbance could impact a patient's perception of quality of life given that, anecdotally, HAE attacks can be abdominal in nature which could potentially result in confusion or an emotional response for those who experience GI related adverse events. The company reported that in the safety population of APeX-2, the proportion of patients with any GI abdominal TEAE was higher in the berotralstat 150mg arm compared to the placebo arm (50.0% versus 35.9%; Table 17 of the company submission, pages 16-17). Although the company reports that all study drug related TEAEs were mild to moderate in severity, we would recommend assessing the EQ-5D data collected within the trial to determine if there is a utility impact around the time of the GI adverse events. We appreciate that the timings of events and collection of EQ-5D data may not align, however the company should at least investigate if the EQ-5D data could be used to support the claim of a minimal impact. |

| | | | |
|---|---|---|---|
| **Additional issue 2:** Insert additional issue | Please indicate the section(s) of the ERG report that discuss this issue | **YES/NO** | Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making |
| **Additional issue N:** Insert additional issue | | | [INSERT / DELETE ROWS AS REQUIRED] |

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## Summary of changes to the company's cost-effectiveness estimate(s)

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|---|---|---|---|
| Insert key issue number and title as described in the ERG report | Briefly describe the company's original preferred assumption or analysis | Briefly describe the change(s) made in response to the ERG report | Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER |
| .. | .. | .. | [INSERT / DELETE ROWS AS REQUIRED] |
| **Company's preferred base case following technical engagement** | **Incremental QALYs: [QQQ]** | **Incremental costs: [£££]** | **Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER** |

# Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

## ERG critique of the company response to technical engagement

**Produced by:** Aberdeen HTA Group

**Correspondence:** Graham Scotland, Reader (Research)
University of Aberdeen, Health Economics Research Unit
Foresterhill, Aberdeen, AB25 2ZD
Email: g.scotland@abdn.ac.uk

**Date completed:** **14 May 2021 (revised AIC/CIC)**

**Contains:** **AIC /CIC**

In their response to the technical engagement report the company addressed each of the issues raised in the ERG report and provided some additional evidence and revised economic analyses. This addendum to the ERG report provides a commentary on the company's response to technical engagement and the revised modelling and highlights any outstanding areas of uncertainty that may need to be considered by the committee. It should be read in conjunction with the company's response document dated 21 April 2021. A set of results incorporating the confidential CMU prices for acute therapies (Berinert, Cinryze, Ruconest and Firazyr) will be provided for the committee in a further confidential appendix.

**ERG commentary on the company's response to technical engagement**

Below the ERG comment on the company's responses to the seven key areas of uncertainty raised in the ERG report.

1. Limited evidence base
2. Selection of data used to inform the model inputs
3. Extrapolation of attack rates beyond the follow-up period of the trial
4. Characterizing uncertainty around the ICER (PSA)
5. The use of utility values from a published study in preference to EQ-5D data collected in the APeX-2 trial
6. The inclusion of carer disutility in the base case analysis
7. The attack costs applied in each arm

***Issue 1 Limited evidence base***

With respect to this issue, the company note that the sample size issue is typical when assessing rare diseases and point out that the APeX-2 trial has a similar sample size compared to trials of other HEA treatments. With respect to additional evidence, the company provide an ad-hoc adjusted analysis of longer-term (96 week) monthly attack rates for the subgroup most closely matching their proposed positioning. This is helpful for confirming an ongoing reduction in the monthly attack rate for responders. However, it is not clear exactly how many patients feed into this analysis. The company noted in their evidence submission form that the 96 weeks data was only currently available for [redacted] of participants.

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

This relates to the ERG's concern regarding the post-hoc subgroup of patients (≥ 2 attacks per month at baseline and previous use of androgens) being used to inform the key inputs in the company's model, particularly the percentage reductions from baseline monthly attack rate. Given the numbers of patients available in this post-hoc subgroup, the ERG originally suggested (at the clarification stage) using the percentage reductions for the ITT population and generalising these to the baseline attack rate for the subgroup of interest. The company argued against this and instead provided scenarios based on the wider pre-specified subgroup of patients experiencing ≥ 2 attacks per month at baseline. The ERG acknowledged in their report that these scenarios may be preferrable over scenarios based on the ITT

population, since they only require the assumption that percentage reductions are generalizable between those with and without prior androgen experience (while providing more data to inform inputs). The ERG suggested that it would be useful to gauge further clinical expert opinion on the generalizability of percentage reductions in attack rate between those with and without previous experience of androgens.

The company have reiterated their argument that the subgroup 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. And they have reiterated their argument against using the ITT population of APeX-2 to inform the percentage reductions in the model. However, the ERG had already acknowledged that the company's proposal to provide scenarios using the larger subgroup (≥2 attacks at baseline) may be preferrable.

With the respect to the request for further clinical opinion on the generalisability of berotralstat efficacy between those with and without prior androgen use, the company have not provided any further insights.

They make a final point that "*rejecting the use of the proposed subgroup positioning on the grounds of small sample size would be inconsistent with precedent set by NICE decisions regarding HAE therapy. In particular, Takhzyro was granted approval in a restricted population based on a small subgroup of patients from the pivotal RCT*." However, the ERG would note that lanadelumab was granted approval based on its comparative efficacy versus placebo (and indirectly versus C1-INH) derived for the ITT population of HELP-03 trial being generalised to a small subgroup of patients with a much higher baseline attack rate. It was for similar reasons that that ERG originally suggested scenarios using percentage reductions derived from the APeX-2 ITT population and applying these to the baseline attack rate for the subgroup meeting the proposed positioning. Note, the ERG was never suggesting applying the baseline attack rate from the ITT population, as this is clearly inconsistent with the company's positioning. The ERG was only suggesting using the wider ITT population to obtain more precise and robust estimates of percentage reductions from baseline.

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

For extrapolation of attack rates beyond the follow-up period of APeX-2, the company originally carried forward the last observed percentage reduction for berotralstat responders and placebo arm patients (SoC). The ERG was concerned that this fails to recognise the random variation in the monthly attack rates, which appears quite substantial given the small patient numbers. The ERG preferred to carry forward the average percentage reductions in attack rate observed over months 0 to 6 for the placebo (SoC) arm patients and over months 4 to 12 for berotralstat responders. The ERG also acknowledged the relevance of the company's alternative analysis of carrying forwards the baseline attack rate in the placebo arm. The ERG suggested it would be beneficial to gauge further expert opinion for the alternative extrapolation approaches for the berotralstat and SoC arms in the context of the company's argument that patients in the placebo arm of APeX-2 experienced a placebo effect in months 1 to 5 which should not be included in the percentage reduction carried forward.

The company have provided some further support for a placebo effect, in the form of clinical expert opinion obtained at a recent advisory board meeting. The company note that the experts identified that the "pattern is in line with findings they have observed from other trials in HAE which have shown a similar pattern in attack rates for placebo patients". Potential mechanisms for the placebo effect that are offered include:

- A decreased sense of stress and anxiety about having an attack, resulting from patients in the placebo group of the double-blind trial believing they were randomised to berotralstat. They further note that after a few months, placebo patients would begin to suspect that they were not on active treatment as their attacks had not significantly decreased, and the placebo effect would begin to wear off. They argue that this could explain the increase observed at month 6 in the placebo arm of APeX-2, which justifies their LOCF approach.
- an improved level of overall care in a clinical trial than in clinical practice, which may have influenced the reduction in attack rate for placebo patients despite the lack of prophylactic therapy.

They further argue that the reduction observed in the placebo arm is unlikely to reflect random variation, as it was observed consistently across months 1-5.

*The ERG welcomes the company's further explanation as to why they believe a placebo affect may be responsible for the reduction seen in the placebo arm of APeX-2, and why this pattern might not be observed in routine practice for patients receiving SoC (acute therapy in demand). However, the ERG still believes that at least some of the reduction seen in the placebo arm of APeX-2 may be regression to the mean, since patients were selected for this subgroup based on an attack rate $\geq 2$ in the month leading up to randomisation. The approach of carrying forward any single monthly attack rate still carries uncertainty given the fluctuation observed in both arms of APeX-2. The company have now carried forward the baseline attack rate in the SoC arm in their revised base case.*

With respect to the extrapolation approach for berotralstat responders, the company refer to the longer term 96-week data that are now available and suggest the sustained efficacy data shows that the placebo effect is not the cause of the improvement in attack rates in the berotralstat arm. They also claim their LOCF approach applied to the 12-month data is conservative since the percentage reduction observed at 24 months is greater.

*The ERG acknowledges the 96-week data, and also believes that this offers support for a sustained response, albeit in a few patients. However, it also highlights the ongoing random variation in monthly attack rates (see Figure 1 of the company response form), which further highlights the risk of introducing bias by carrying forward any single percentage reduction in the monthly attack rate (ranging from approximately [redacted] in the adjusted 96 week data). Therefore, the ERG believes that carrying forward the average percentage reduction offers a more robust approach for the berotralstat arm, as the company have done in their revised base case.*

***Issue 4 Characterizing uncertainty around the ICER (PSA)***

This relates to the company's PSA, which originally used a value of 10% to represent standard errors around the percentage reductions in attack rates applied in the model. The ERG was concerned this may have under-represented the uncertainty given the small number of patients informing the model. However, the company argued that the application of standard errors based on the data, results in variation that is too extreme "for any true impact of uncertainty to be identified". In response to technical engagement, the company have provided a further analysis in which they assume standard errors of 20%.

Upon reflection, the ERG believes that while the standard errors based on the data may be large, this reflects the fact that the model inputs have been informed a small subgroup of patients. Nevertheless, given the knowledge of a significant reduction in attack rate versus placebo in the overall ITT population, there is potential for the standard errors in the subgroup to overplay the uncertainty. This relates to issue 2, in which the ERG argue that more precise and robust estimates of percentage reductions could have been obtained from the larger prespecified subgroup or the ITT population, and applied (generalised) to the baseline attack rate for the sub-population of the positioning. However, the company appear to want all the inputs, including the percentage changes in attack rates, to be based on the smaller subgroup meeting the positioning, but then approximate the uncertainty around those inputs rather than relying on the standard errors based on the actual data used.

The ERG has identified further issues with company's PSA, in that the percentage changes in attack rate are assigned lognormal distributions and constrained to be either positive or negative in line with the point estimate. This is inappropriate because the uncertainty around some of the percentage changes from baseline attack rate should encompass both increases and reductions. Further, the company approach of assuming a standard error of 10% or 20% of the observed percentage change, results in the modelled uncertainty being proportional to the observed reductions; i.e. it gives the false impression that smaller percentage changes are much more certain that larger percentage changes.

Overall, the ERG does not believe that any of the PSAs provided by the company provide an accurate representation of the decision uncertainty, but it has not been able to offer an alternative given the data provided. In particular, the standard error for the average percentage reduction in attack rate, carried forward in the model, was not provided.

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

This relates to the ERG's opinion that use of the EQ-5D data from APeX-2 should have been explored more thoroughly given these data are collected directly from APeX-2 trial participants, and so could be more applicable to the attacks included the model (also base on APeX-2).

The company have explored the EQ-5D data in the larger subgroup and the ITT population by whether an attack was ongoing at the time of the assessment, but they have only provided mean values by observation time point (See Tables 5 and 6 of the company's technical engagement response). They do not provide the number of observations available or any other information about the nature of the data. Rather, they reject using it because the mean utility values for attack free are above the UK population norms. The ERG is not satisfied that this is a valid argument for rejecting the data, as the ERG proposal was to use the data to inform the difference in attack and attack free utility using a regression framework. A simple comparison of the mean estimates for 'attack ongoing' and 'attack free' shows the difference between them [redacted] utility decrement applied in the company model based on the data reported by Nordenfelt et al. However, it is possible that the EQ-5D data available for ongoing attacks from APeX-2 is not representative of the average attack. For example, those with mild attacks may have been more likely to provide data during an ongoing attack, which could bias the utility estimate for attacks upwards. Given the lack of detailed exploration and discussion of the data, it is difficult to say. However, the ERG acknowledge that the utilities based on Nordenfelt et al. were accepted in previous NICE appraisal of lanadelumab.

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

The ERG questioned the company's justification for including carer disutility in their base case analysis. The company have reiterated their case that HAE attacks are very disabling for patients over their duration, and consequently confer a significant burden on carers in terms of providing physical support. They also note the hereditary nature of the condition, meaning that many carers are also HAE patients, and subsequently suffer anxiety about their own attacks as well as the attacks of those they are caring for. The company also note that they only apply carer disutility for the duration of attacks and that this is conservative since it does not capture a potential general reduction in carer anxiety associated with a reduced frequency of attacks in the person they are caring for. Nevertheless, the company appear to acknowledge the potential for overestimating carer disutility caused by applying it to all acute attacks and have modified their assumptions to only include it for 52.4% of attacks. This is based on the percentage of patients who reported receiving assistance from a caregiver during their last attack in a published European burden of illness study (Caballero et al. 2014).

The ERG believe that the company's revised case is more realistic, but still have some concerns regarding the magnitude of the disutility estimate, and the assumption that it would apply for the entire duration of attacks. Limited details on the methods of the TTO study used to derive the carer disutility were provided by the company. Participants from the UK general population provided TTO values for a vignette describing carer burden. However, participant numbers and demographics were not provided, and the ERG have not seen the vignette that was presented to participants, or interview schedule describing the way the question was framed. This makes it difficult to gauge potential for bias in the estimate.

***Issue 7 The attack costs applied in each arm***

The ERG was uncertain with respect to the evidence supporting different treatment costs for acute attacks in the separate arms of the model, and that this might be a chance finding due to small numbers in the post-hoc subgroup informing the model estimates. Therefore, the ERG suggested that the company explore this issue further by looking at the difference in treatment costs between those assigned to berotralstat and SoC in the ITT population of APeX-2 and seeking further clinical opinion on the use of multiple treatments in routine practice.

The company have provided a breakdown of the proportion of attacks treated with a single dose and multiple doses of acute therapies in each arm of APeX-2. This has been provided for the post-hoc subgroup (≥2 attacks per month and previous androgen use at baseline), the larger subgroup (≥2 attacks per month) and the ITT population. These do show that the proportion of attacks treated with two or more doses is consistently higher in the SoC (placebo) arm. Clinical opinion sought by the company also suggests a plausible mechanism by which those on prophylaxis may be expected to require fewer multiple administrations of acute treatment; i.e. lower background levels of bradykinin production, making it easier to either avert clinically manifested attacks or limit their severity and duration.

Given the data presented, the ERG accepts the application of different acute treatment costs by treatment arm but would note that the absolute magnitude of the cost in each arm is also important. Of the available estimates from APeX-2 (company response, Table 10), the post-hoc subgroup (used to inform the model) provides the highest estimated proportions of treated attacks requiring multiple administrations of acute therapies; [redacted] and [redacted] in the berotralstat and SoC arms respectively. Responses from other consultees quote other sources for the percentage of attacks treated with icatibant which required multiple doses.

In an open label extension (OLE) of the FAST-1 trial of icatibant, 88.2% of icatibant treated attacks used a single administration (300/340), 10.6% used 2 administrations, and 1.2% used three administrations. A further 5.3% (18/340) of attacks required some further rescue medication, although only four patients received C1-INH. In the OLE of FAST-2, most attacks (89.8%) were treated with a single icatibant injection; with 10.2% receiving further administration(s) of icatibant and a further 2.9% receiving some other rescue medication (types not reported). In the OLE of FAST-3, it appears that only 3% of icatibant treated attacks received a repeat dose. In a UK cohort included in the Icatibant Outcomes Survey (IOS), Longhurst et al reported that 12.7% of icatibant treated attacks required rescue medication with C1-INH. However, the percentage of attacks requiring multiple icatibant doses was not reported. Caballero et al. on the other hand, reported that of 335 icatibant treated attacks in 45 UK patients, 38 (11.3%) received a second

icatibant dose. Of note, UK patients who were not on prophylactic treatment appeared to have a higher retreatment rate at 23.3% (20/86), which supports the company's assertion that prophylaxis influences the amount of acute therapy required. However, this finding was not consistent across countries, with the overall rate of repeat icatibant treatment (per attack) very similar between those on and not on prophylactic treatment (9.4% and 10.2%) when considering the combined data from 5 European countries.

Whilst the above data do not provide a full picture of the proportion of all attacks requiring multiple doses of acute therapies in UK practice, they do suggest the percentages from APeX-2 may be quite high in relation to some alternative sources. Generalisability of acute treatment costs based on the data from APeX-2 remains an area of uncertainty. However, they are consistent with other attack data included in the model which are also sourced from APeX-2.

**Further ERG scenarios**

The ERG has provided some further scenarios around the company's revised base case assumptions, to further explore remining uncertainties around the source of data used to inform the model inputs (larger subgroups versus restricted subgroup), the extrapolation of the monthly attack rate in the SoC arm, and the inclusion of carer utilities. The results of these are provided in Table 1 (≥ 2 attacks per month and previous use of androgens subgroup), and Table 2 (≥ 2 attacks per month subgroup).

It can be noted that carrying the average observed attack rate forward for the SoC arm (rather than the baseline attack rate) has the largest impact on the ICER (scenarios 1 and 4). Using data from the larger subgroup (≥ 2 attacks per month) to inform the baseline attack rate, percentage reductions in attacks, and attack treatment costs (and otherwise accepting company base case assumptions), also results in a substantial increase in the ICER (scenario 3). It can be noted, however, that this increase is primarily due to the lower average pooled baseline attack rate in the larger subgroup ([redacted] versus [redacted]). If the higher baseline attack rate for the smaller subgroup (≥ 2 attacks per month and previous use of androgens) is maintained in the model whilst using data from the larger subgroup to inform percentage reductions in attack rates and attack treatment costs, the ICER increases by only a modest amount (scenario 6) compared to the company base case. This may be relevant because it is possible that those with prior experience of androgen prophylaxis really do have a higher baseline attack rate (i.e. these patients received previous prophylaxis because they experienced a higher frequency of attacks) and the difference is not just due to chance. That said, the smaller subgroup is not an exact match for the proposed positioning in those experiencing two or more attacks per month: "HAE type I or II patients who experience two or more attacks per month and are unsuitable or refractory to androgens. The ERG note that previous use of androgens does may not necessarily mean that all these patients were unsuitable for or refractory to androgens.

**Table 1 ERG's further analysis around the company base case**

| Scenario | Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER incremental (£/QALY) | % change from CS Base case |
|---|---|---|---|---|---|---|---|---|---|
| 0 | **Company Base Case (April 2021)** | | | | | | | | |
| | SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | - | |
| | Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 69,908 | 0.0% |
| | **ERG further analyses** | | | | | | | | |
| 1 | **SoC: average attack rate over months 0-6 to carried forward** | | | | | | | | |
| | SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | - | |
| | Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 179,874 | 157.3% |
| 2 | **No carer disutility applied** | | | | | | | | |
| | SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | - | |
| | Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 80,813 | 15.6% |

**Table 2 ERG's further analyses using data inputs from the larger subgroup (≥ 2 attacks per month at baseline)**

| Scenario | Technologies | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER incremental (£/QALY) | % change from CS Base case |
|---|---|---|---|---|---|---|---|---|---|
| 3 | **≥ 2 attack per month subgroup used to inform the baseline attack rate, percentage reductions in attack rates, and attack treatment costs (otherwise company base case assumptions)** | | | | | | | | |
| | SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | - | |
| | Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 121,910 | 74.4% |
| 4 | **As per scenario 3, but with the average percentage reduction in monthly attack rate over months 0-6 (≥ 2 attack per month subgroup) carried forward for SoC** | | | | | | | | |
| | SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | - | |
| | Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 395,816 | 466.2% |
| 5 | **As per scenario 3, but no carer disutility** | | | | | | | | |
| | SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | - | |
| | Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 141,243 | 102.0% |
| 6 | **As per scenario 3, but with the pooled baseline attack rate maintained at [redacted] per month (as per the subgroup with ≥ 2 attacks per month and previous use of androgens at baseline)** | | | | | | | | |
| | SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | - | |
| | Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 74,306 | 6.3% |
| 7 | **As per scenario 6, but with the average percentage reduction in monthly attack rate over months 0-6 ≥ 2 attack per month subgroup carried forward for SoC** | | | | | | | | |
| | SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | - | |
| | Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 337,266 | 382.4% |
| 8 | **As per scenario 6, but with no carer disutility applied** | | | | | | | | |
| | SoC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | - | |
| | Berotralstat | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | 86,090 | 23.1% |

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