Public observer slides - redacted

PART 1

NICE National Institute for Health and Care Excellence

Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

Lead team presentation

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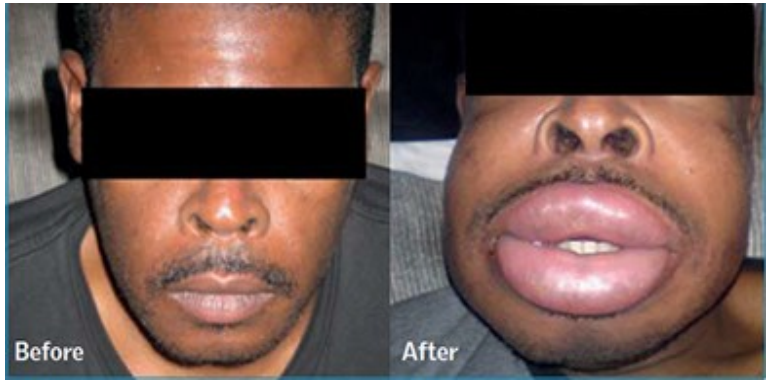
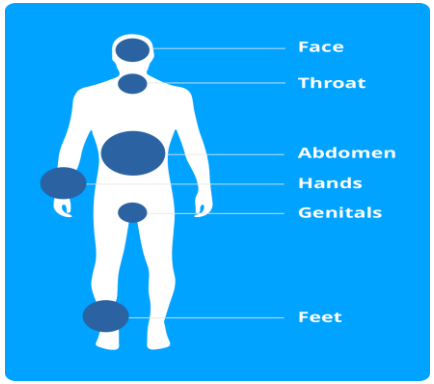
Company: BioCryst Pharmaceuticals

ACM1: 16th June 2021

Hereditary angioedema (HAE)

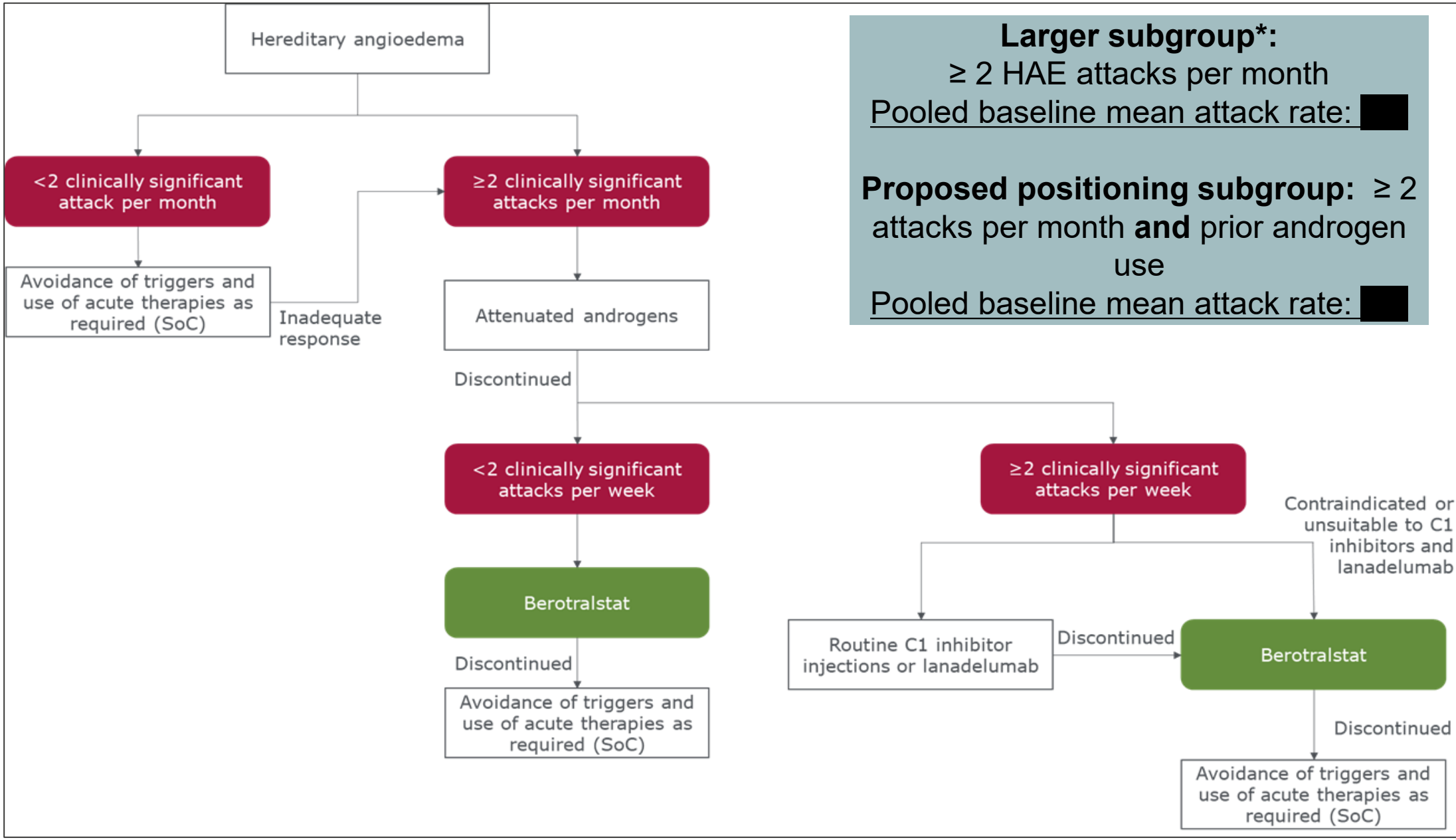
- HAE is a rare genetic disorder ➔ affects between 1 per 50,000 to 1 per 100,000 of the population
- Most cases develop during the first 10 to 20 years of life ➔ Annual attack frequency is highly variable with some people experiencing more than 20 attacks per year.
- Three subtypes:
  - **Type I and Type II** ➔ SERPING1 gene mutation
  - Type III ➔ normal C1-INH
- It is a relapsing disorder which can cause severe pain, affect quality of life and potentially be life threatening ➔ marked with spontaneous recurrent attacks of swelling
- In patients with HAE the function of the C1-esterase inhibitors (C1-INH) is insufficient ➔ accumulation of excessive fluid (oedema) and localised swellings
- HAE can affect single or multiple anatomical sites simultaneously ➔ unpredictable episodic swelling usually occurs in the mouth, the gut and the airway, causing difficulty with breathing (with potential asphyxia) and severe pain in the stomach





Abdominal swelling during an HAE attack

Treatment pathway



Source: adapted from Berotralstat BioCryst Evidence submission v4.0, Figure 1

* APEX-2 ITT population included people who had at least 2 attacks in the last 2 months

Patient expert perspectives (1)

Submissions from HAE UK

- Attacks are unpredictable and sporadic ➔vary in severity from mild to life threatening
- Subcutaneous swelling can occur in multiple organs ➔ reach a very large size in approximately 30-40 minutes and take 2 or more days to resolve if left untreated
- No confirmed triggers ➔ common triggers emerge such as hormonal changes, stress and anxiety due to invasive procedures such as dentistry, minor surgery and infections
- Attacks severely impact quality of life (QoL)
  - ability to self-care severely impacted (wear shoes, change clothes, use writing equipment and tablets)
  - Families of children with HAE have to develop a number of strategies for school life, sports, trips away as well as avoidance of certain triggers
  - Unpredictable HAE attacks can affect every area of life ➔ uncertainty requires carrying emergency medication when travelling

'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'

'having this disease has taken my life; my education, my prospect of a career, having a family'

'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'

Patient expert perspectives (2)

- Current treatments stop swelling progressing but unable to resolve it
  - most effective treatments for HAE are injectable products
  - existing oral products are only effective in the least badly affected patients and still requires intravenous C1-INH rescue
  - Many C1-INH users attend A&E in order to be infused ➔ cannot self cannulate
  - Icatibant is considered unpleasant to use and often deferred for advanced attacks

'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'

'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'

- The advance of an effective oral product is regarded as the 'Grail' by many patients
  - a single, daily tablet dosing is convenient and unobtrusive
    - no need for special training for patients
    - benefit for patients who are needle phobic
  - no concerns about supply or fluctuations in the market (worldwide shortage of danazol)

Clinical expert perspectives

Submissions from BSACI, RCPth and UKPIN

- Treatment individualised with aim of prophylaxis to reduce attacks ➔ allow patient to become attack free
- Prophylaxis treatment is considered if ≥1-2 HAE attacks occur per month
  - Currently, there is no effective licensed oral prophylaxis
  - Injectables are restricted to patients with extremely severe disease ➔ leaves a large cohort of patients with moderate to severe disease
- Attenuated androgens are associated with side effects, contraindications and supply issues
- C1-INH is used in line with the NHS England commissioning policy.
  - It is primarily used as short-term prophylaxis (for example before surgery) ➔ rarely long term prophylactic use
- Berotralstat is custom designed for prevention of swelling attack
  - Accessible to anyone with frequent attacks
  - Improve quality of life and reduce burden of other treatments
  - Healthcare resource use may decline ➔ A&E attendance and hospital treatment
  - Reduction in number of attacks ➔ reduced use of injectables for treatment of acute swelling
  - Effective prophylaxis for patients with HAE who do not qualify for prophylactic treatment with C1 inhibitor or lanadelumab

Berotralstat (Orladeyo, BioCryst Pharmaceuticals)

Mechanism of action	Berotralstat is a small-molecule inhibitor of plasma kallikrein – a precursor of bradykinin.
Marketing authorisation (MA)*	'Orladeyo is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older' (MA granted 30 April 2021)
Administration	Orally, 150 mg once daily.
List price†	[redacted] per 1 capsule of 150 mg or [redacted] per pack of 28 capsules or [redacted] per annum). The company has a patient access scheme (PAS). With the PAS the annual cost is estimated to be [redacted].

Berotralstat was granted Early Access to Medicines Scheme (EAMS) status

- Gives patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a MA when there is a clear unmet medical need.
- EAMS therapeutic indication for berotralstat was: 'for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older'

<u>* Company's positioning: ≥ 2 attacks per month and prior androgen use</u>
Danazol is frequently used androgen, but there is a worldwide supply problem. If committee recommended berotralstat per company positioning, would this inadvertently prevent some people accessing treatment?

Background

Population	**Company:** Patients aged ≥ 12 years with HAE who experience ≥ 2 attacks per month and are unsuitable for or refractory to androgens **NICE Scope:** People aged 12 years and older with HAE
Clinical trial	APEX-2 RCT (N=121) – Part 1 of 3 part trial only relevant for this appraisal • berotralstat vs. placebo in people ≥ 12 years with type I or II HAE and at least 2 attacks in last 2 months • **Part 1: Berotralstat:** 110 mg (n=41) and **150 mg (n=40), Placebo (n=40)**
Intervention	Berotralstat 150mg arm from Part 1 of APEX-2
Comparators	Standard of care (SoC) – defined as treatment on demand for acute attacks • Placebo arm from part 1 of APEX-2

Key results* (Mean attacks per month)

Month	0	1	2	3	4	5	6	% reduction - berotralstat vs placebo
BERO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-44.2% [redacted]
SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Model	Cohort model, 2 health states: 'Alive with HAE' & 'Dead' • Continuation rule: people with ≥ 50% reduction in attack rate after 3 months versus baseline continue to receive berotralstat

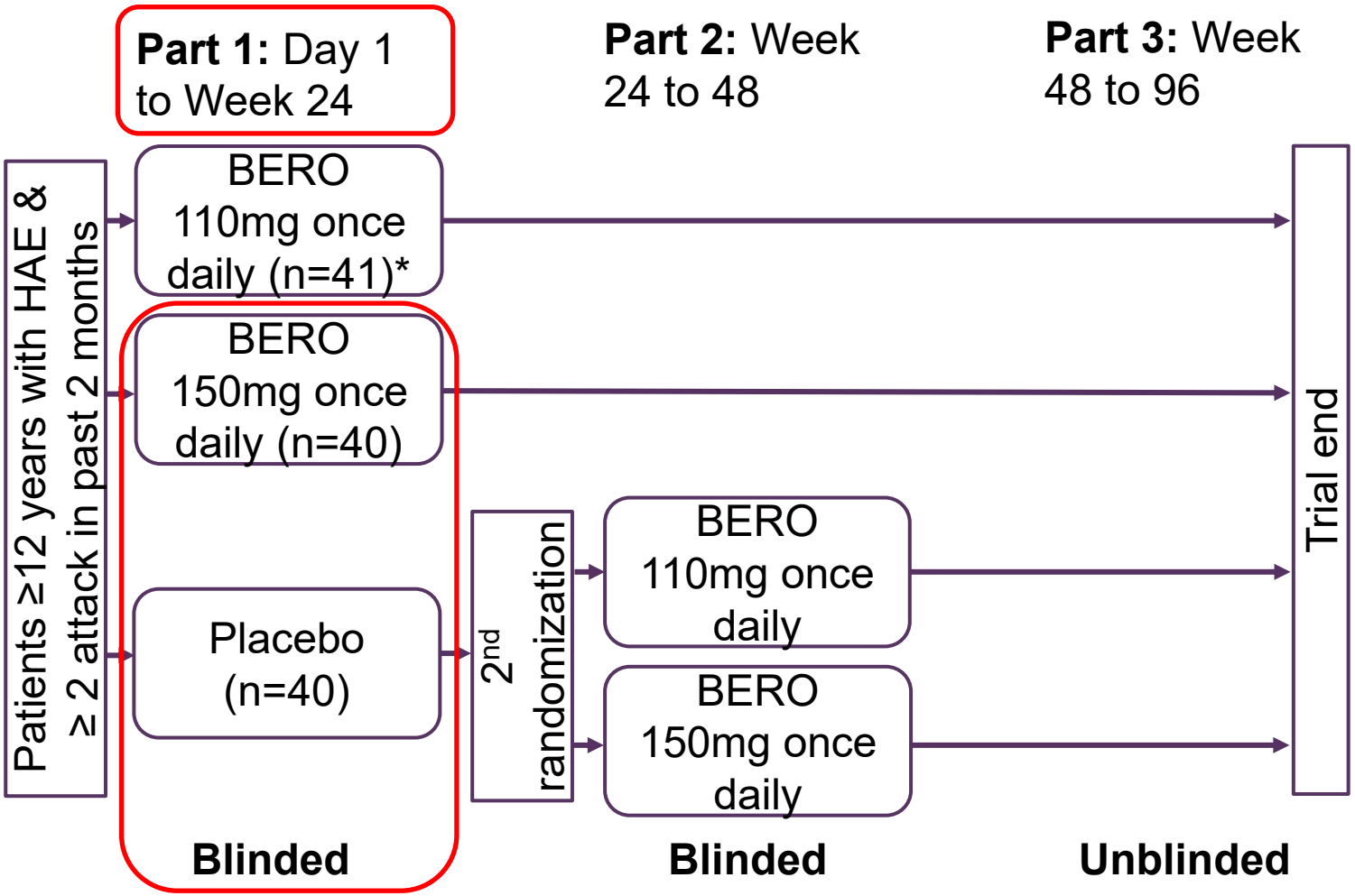
RCT randomised controlled trial

***ITT population, without a stopping rule**

Clinical evidence summary (1)

Direct clinical trial evidence

APEX-2 RCT



N=35 in the company's proposed positioning subgroup (≥ 2 attacks per month and prior androgen use) used in the economic model. This was based on 17 patients in the berotralstat arm and 18 patients in the placebo arm

*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

Clinical evidence summary (2)

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

Source: adapted from Berotralstat BioCryst Evidence submission v4.0, Figure 4

Clinical evidence summary (3)

Investigator-confirmed attack rate (mean)							
Month	Baseline	1	2	3	4	5	6
Berotralstat *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline (%)							
Berotralstat *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

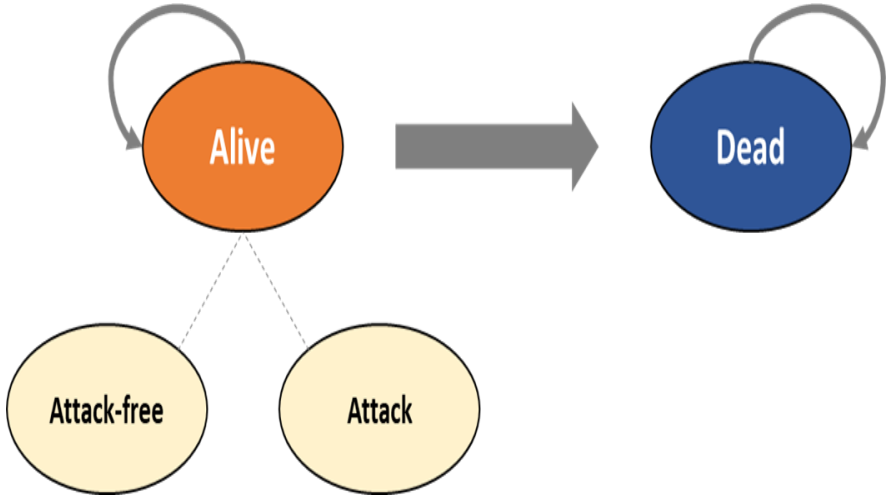
Berotralstat 150mg; N=40	Placebo; N=40	Berotralstat vs Placebo % (95% CI)
Rate per 28 days	Rate per 28 days	
1.31	2.35	-44.2% [redacted], p-value [redacted]

*Economic model includes responder-based continuation rule in berotralstat arm not shown here

Cost effectiveness summary (1)

Company model

- Cohort approach with 2 heath states ➔ 2 sub-states
- Population: ≥ 2 attacks per month and prior androgen use (proposed positioning subgroup)
  - Scenario analysis provided for a larger subgroup ➔ ≥ 2 attacks per month only
- Time spent in 'attack-free' and 'attack' sub-states was determined by treatment-specific attack rates and the duration of attacks as observed in APeX-2
- Continuation rule applied in the economic model (see slide 13)



Source: Berotralstat BioCryst Evidence submission v4.0, Figure 11

- 28 days cycle length aligns with half cycle correction
- 56-year (lifetime) horizon, starting age 44 years
- Discount rate 3.5% for costs and health benefits
- Carer disutility included to reflect the burden on carers of people experiencing HAE attacks
- Model drivers: 1) baseline attack rate, 2) averaging of SoC attack rate reduction, and 3) attack costs applied in each treatment arm

Cost effectiveness summary (2)

Continuation rule

- 57.5% of berotralstat patients experienced a ≥ 50% relative reduction in attack rate from baseline ➔ in comparison, 25% of placebo patients experienced a ≥ 50% relative reduction in attack rate from baseline.
- Therefore, company applied a treatment continuation rule in its economic model:
  - **'only patients who achieve ≥ 50% reduction in attack rate by 3 months versus baseline continue treatment with berotralstat'**

- A Delphi panel process conducted by the company was used to generate consensus from the advisory board for the parameters used to inform the continuation rule.

- Continuation rule is not included in APEX-2 or the MA wording.

- Applying the continuation rule further reduces the berotralstat sample size (n=8).

How appropriate is the continuation rule applied in the company model to clinical practice?

Cost effectiveness summary (3) - Modelled results

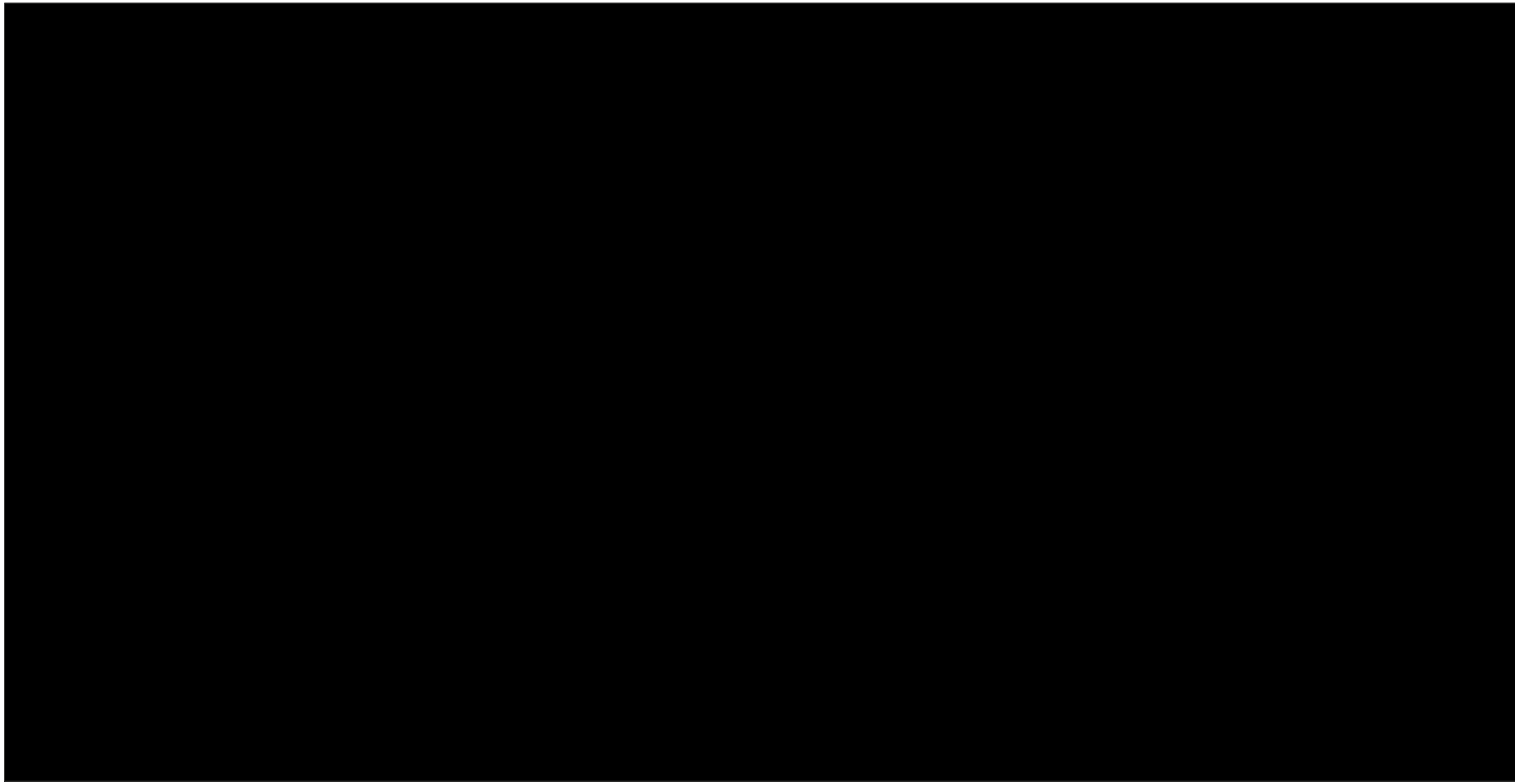
Proposed positioning subgroup experiencing ≥ 2 attacks per month at baseline with prior experience of androgens*

[redacted]

NICE *Proposed positioning subgroup, with continuation rule applied to responders

Cost effectiveness summary (4) - Modelled results

Larger subgroup experiencing ≥ 2 attacks per month at baseline*



NICE * Larger subgroup, with continuation rule applied to responders

Issues unresolved post technical engagement

Key issues unresolved post technical engagement	Status	Impact	Slide
Issue 1: Limited evidence base • Is the evidence base from APEX-2 sufficient for decision making?	**To discuss**		17
Issue 2: Selection of data used to inform the model inputs • Is the ITT population more appropriate than the proposed positioning subgroup to inform cost-effectiveness inputs? • Which baseline attack rate should be used in the model	**To discuss**		18-19
Issue 3: Extrapolation of attack rates beyond trial follow-up period • How should attack rate be applied beyond the trial follow up period?	**To discuss**		20-22
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Issue 6: The inclusion of carer disutility in the base case analysis • Is it appropriate to include carer HRQoL impact? If so, how should this impact be quantified?	**To discuss**		24
Issue 7: The attack costs applied in each arm • Should equalised attack costs be used for berotralstat and SoC?	**To discuss**		25-26

Key: Model driver  Unknown impact;  Small/moderate impact 

Issue 1: Limited evidence base

Background

- Main clinical evidence is from APEX-2 – N=80 (berotralstat 150mg, n=40; placebo, n=40)
  - Primary outcome (rate of investigator confirmed HAE attacks) assessed at week 24
- **ERG:** Clinical effectiveness is based on one trial with small sample size and limited follow-up ➔ sample size in the model exacerbated by proposed positioning subgroup (placebo n=18, berotralstat starters n=17) and continuation rule (berotralstat responders n=8)

Company:

- Sample size from APEX-2 is similar to studies of other treatments in HAE
  - Cinryze, Haegarda, and Takhzyro trials had 22, 90, and 125 participants, respectively

Clinical experts:

- Difficult to do large trials in this disease ➔Evidence from APEX-2 is representative of HAE in UK clinical practice
- 24 months should be sufficient to capture the key outcomes

Patient experts:

- Not unusual in conditions such as HAE which is very rare ➔ incidence circa 1:50,000

ERG critique:

- Ad hoc analysis confirms an ongoing reduction in the monthly attack rate for responders
  - 96 weeks data was only currently available for [redacted] of proposed positioning subgroup

Is the evidence base from APEX-2 sufficient for decision making?

Issue 2: Selection of data to inform the model inputs

Background

- Company's model inputs are based on subgroup of patients from APeX-2 meeting company's proposed positioning ➔ ≥ 2 attacks per month and prior androgen use
- **ERG:** model is driven by percentage reductions from baseline attack rates for berotralstat and SoC arms ➔ using proposed positioning subgroup and application of continuation rule results in the model inputs being based on data from a small number of patients
  - N=35, 17 berotralstat patients and 18 placebo patients
  - Treatment continuation rule further reduces berotralstat sample size to n=8
  - Suggest relative reduction in attack rates to be based on a larger trial population ➔ intention to treat (ITT) population

Company:

- Using the ITT population includes patients who would not receive berotralstat in the UK.
- Using the ITT data substantially increases the cost-effectiveness estimate because berotralstat is more effective in the proposed positioning subgroup
- Rejecting the use of the proposed subgroup positioning on the grounds of small sample size would be inconsistent ➔ Takhzyro (lanadelumab) was granted approval in a restricted population based on a small subgroup of patients from the pivotal trial

Issue 2: Selection of data to inform the model inputs

Clinical experts:

- Would not expect prior androgen treatment to make a difference with a sufficient wash out period
- However, patients with prior androgen use may not be the same as patients without prior androgen use ➔ may have had severe disease to start with

ERG critique:

- Company did not provide further insight into generalisability of berotralstat efficacy between those with and without prior androgen use.
- Lanadelumab was granted approval based on 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
- ERG suggest using the relative reductions from the ITT population, but the baseline attack rates from the proposed positioning subgroup

Is the ITT population more appropriate than the proposed positioning subgroup to inform cost-effectiveness inputs?

- **Which baseline attack rate should be used in the economic model?**

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

Background

- Observed data for the subgroup of APeX-2 informs monthly percentage reductions in attack rates from baseline to 12 months for berotralstat, and to 6 months for SoC
  - Used the last observed carried forward (LOCF) to extrapolate attack rates beyond the follow-up period of the trial
- **ERG concerns:**
  1. Use of unadjusted baseline attack rates
  2. Percentage reductions for berotralstat responders calculated relative to baseline attack rate of wider subgroup
  3. LOCF fails to recognise the observed variation in monthly attack rates compared to baseline ➔ may exaggerate the expected difference in the attack rate between the berotralstat and SoC arms
- **ERG's suggestions:**
  1. Set the baseline attack rates equal between treatment arms
  2. Apply mean percentage reductions for responders relative to the baseline attack rate of the responders
  3. Carry forward the average % reduction in monthly attack rate rather than last observation ➔months 4-12 for berotralstat responders and months 0-6 for SoC

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

Company:

- Adjusted base case as follows:
  - Pooled baseline attack rate between berotralstat and SoC ➔ ✓
  - Separate baseline attack rate for berotralstat responders ➔ ✓
  - Average reduction in attack rate over months 4-12 is used from month 12 onwards for berotralstat arm relative to baseline attack rate for berotralstat responders ➔ ✓
  - For SoC: The reduction in attack from baseline beyond 6 months is set to 0% ➔ ✗

Clinical experts:

- Using baseline attack rate for responders removes potential variation ➔ sample size issue
- For berotralstat, it is unlikely that there will be a lot more change after 3 months of follow-up
- Reduction in SoC attack rates likely because of placebo effect, natural variation and regression to mean ➔ size of impact not known
- Reasonably appropriate to carry forward the baseline attack rate for the remainder of the model time horizon for the SoC arm
- Attack frequency to be relatively consistent from month to month in both arms ➔ some variability across individuals due to external factors such as stress.

Key: ✓ - ERG suggested ✗ Not ERG suggested

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

ERG critique

- Company's revised base case considered more robust
- Welcomes further explanation of placebo effect resulting in attack reduction in the placebo arm of APeX-2
  - Still believes that at least some of the reduction seen may be regression to the mean
  - Carrying forward any single monthly attack rate still carries uncertainty given the fluctuation observed in both arms of APeX-2
- Acknowledges the 96-week data from the proposed positioning subgroup supports sustained response, albeit in a few patients ➔ Not used in the model
  - However, it highlights ongoing random variation in monthly attack rates ➔ risk of introducing bias by carrying forward any single percentage reduction

How should attack rate be applied beyond the trial follow up period?

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

Background
- Utility values based on published study in Swedish patients (Nordenfelt et al 2014)
- **ERG:** EQ-5D data directly from APEX-2 should have been explored further, particularly in full ITT population given the small sample size of proposed subgroup

Company:
- Nordenfelt et al., (2014) utility values have previously been accepted by NICE in the appraisal of lanadelumab (TA606) in HAE

Clinical expert:
- EQ-5D may not be the most appropriate measure to assess QoL in HAE.
- The HRQoL impact of an attack is more likely to be driven by personal factors and severity, rather than prior treatment or attack rate
- Would expect QoL in berotralstat arm to be better compared to SoC arm when attack free.

ERG critique:
- Acknowledge that Nordenfelt et al. utilities were accepted in TA606
- Not a valid argument to reject EQ-5D data because the mean utility values for attack free are above the UK population norms
- It is possible that EQ-5D data for ongoing attacks is not representative of the average attack
- Provided additional scenario using utility decrements for attacks based on observed EQ-5D data from APEX-2 trial

Is it appropriate to use utility values from Nordenfelt et al., (2014) instead of EQ-5D from APEX-2?

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

Background

- Model includes caregiver disutility based on a time trade off (TTO) study which reflects impact on caregivers due to anxiety and need to provide care
- **ERG:** No strong case was not made to include a carer disutility in the model
  - Including carer disutility reduces the QALYs in the SoC arm more than berotralstat arm

Company:

- Amended base case with disutility applied to 52.4% of attacks (Aygören-Pürsün et al., 2014)

Clinical expert:

- Difficult to establish the magnitude of impact on carers
- Expect carer disutility in HAE to be lower than for severe Alzheimer's disease

Patient expert:

- Impact of HAE on carers often underestimated ➔ suffer same anxiety as the patients
- Often, carers (typically female) have given up career to be available to care during attacks

ERG critique:

- Revised base case more realistic but concerns regarding the magnitude of the disutility estimate remain
- Limited details on the methods of the TTO study provided

Is it appropriate to included carer HRQoL impact? If so, how should this impact be quantified?

Issue 7: The attack costs applied in each arm

Background

- The cost per attack is estimated to be lower in the berotralstat arm ➔ reduced need for multiple administrations
- **ERG:** clinical advice suggests no plausible reason for prophylactic treatment to consistently impact on the cost of treating attacks ➔ Difference possibly due to random variation
  - Equalised attack costs across the treatment arms substantially increased the ICER
  - Data from ITT population would increase the sample size and reduce uncertainty

Company:

- Use of acute treatments in the berotralstat and SoC arms of APeX-2 is consistent between proposed subgroup and the ITT population and ≥2 attacks at baseline populations
- Clinical advice suggests 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

Stakeholder:

- Provided alternative published data sources that may help inform the acute therapy usage
  - C1-INH used as rescue in 12.7% of icatibant-treated attacks (Longhurst et al. 2018)
  - Icatibant injection usage: One: 88.2%, Two: 10.6%, three: 1.2% (Malbrán et al. 2014)
  - 89.8% attacked successfully treated with single icatibant injection (Baş et al. 2013)

Issue 7: The attack costs applied in each arm

Clinical expert:

- Would expect prophylactic treatment to reduce both the frequency and severity of HAE attacks ➔ result in lower costs per attack overall
- Would expect the number of people who require a second dose of treatment to reduce if berotralstat reduces attack severity

ERG critique:

- Accepts the application of different acute treatment costs by treatment arm
- Consultees quote other sources for the percentage of attacks treated with icatibant which required multiple doses ➔ suggests the percentages from APeX-2 may be quite high in relation to alternative sources
- Generalisability of acute treatment costs based on the data from APeX-2 remains an area of uncertainty

Should equalised attack costs be used for berotralstat and SoC?

Other considerations

Innovation

- First orally available targeted kallikrein inhibitor for prevention of HAE attacks
- 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.

Equality

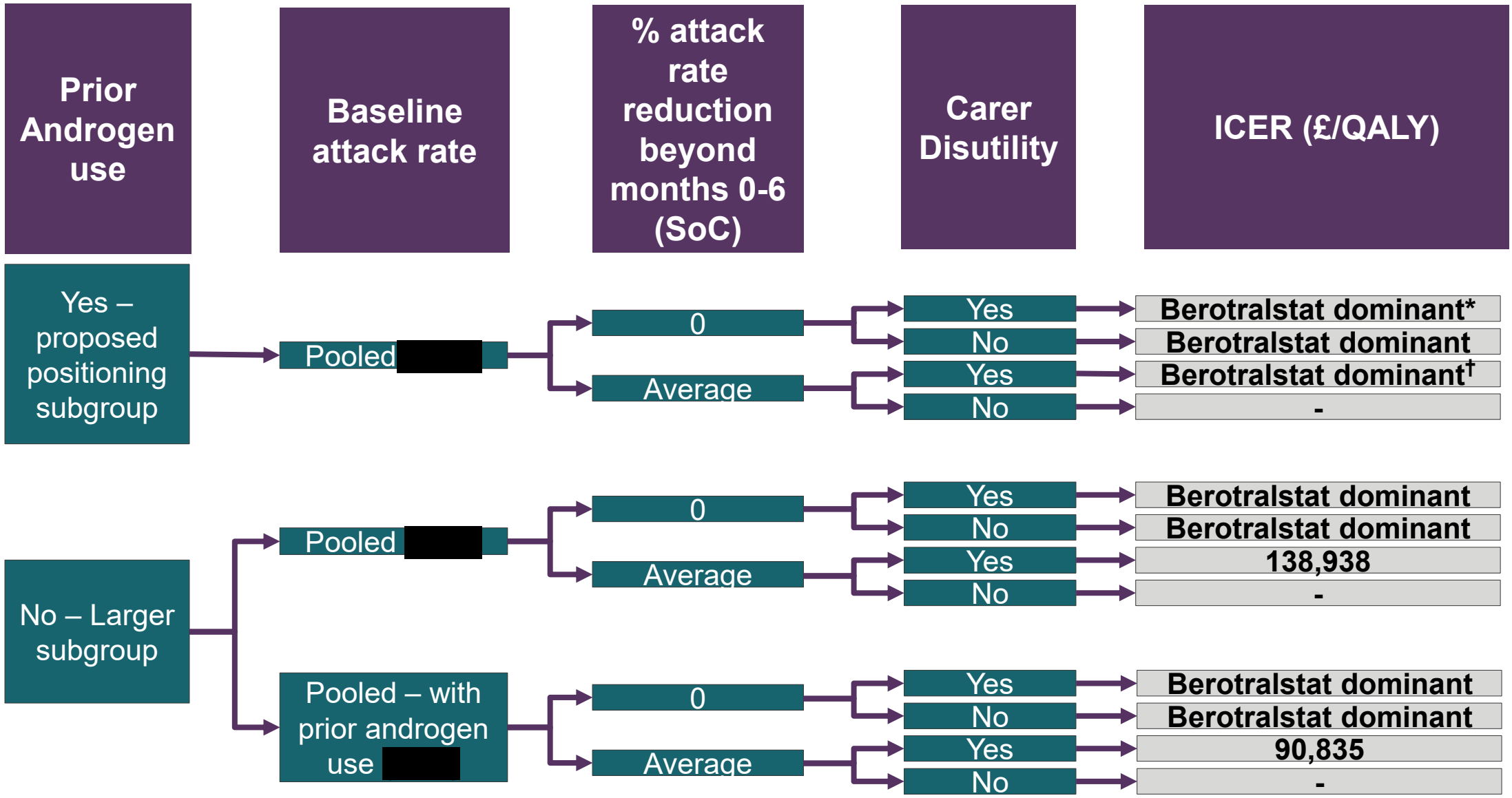
- No equality issues identified

Potential recommendations

- Company proposed positioning is after androgens (or if they are unsuitable)
- Most used androgen is danazol, but there is a worldwide shortage
- If committee recommends per company positioning, could this inadvertently prevent some people accessing treatment?

- **Is berotralstat an innovative treatment for preventing acute attacks of HAE?**
- **Are there any additional benefits with berotralstat that have not been captured adequately in the economic model?**
- **Are there any equality issues relevant to this appraisal?**

Cost-effectiveness results: Berotralstat PAS only[#]



* Company's base case ICER

† ERG's base case ICER

[#]All ICERs with comparator PAS (cPAS) will be presented in part 2

NICE

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Cost-effectiveness results:
Additional ERG scenario – PAS price

- The ERG conducted a further scenario, which uses an alternative value for the utility decrement associated with acute attacks.
- ***Utility decrement for attacks*** **=** *difference between mean observed utility while attacks ongoing minus mean observed utility when attack free in APeX-2* [redacted] *using EQ-5D*

Technology	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
SoC	-	-	-
Berotralstat	[redacted]	[redacted]	**Berotralstat dominant**

ERG comment:

- plausible that the difference underestimates the true average utility decrement of attacks observed during APeX-2
  - difference is unadjusted for individual's attack free utility, and the capture of EQ-5D during attacks appears to have been sporadic in APeX-2
  - potential for bias if EQ-5D responses coinciding with attacks were more likely to be obtained during mild attacks