NICE National Institute for Health and Care Excellence

Berotralstat for preventing acute attacks of hereditary angioedema [ID1624]

Chair's presentation

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Company: BioCryst Pharmaceuticals

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Key issues for consideration

Key issues remaining post consultation	Impact
1. Limited evidence base and selection of data used to inform the model inputs	
2. Extrapolation of attack rates beyond trial follow-up period	
3. Acceptability of a treatment continuation rule in clinical practice	
4. Attack severity not reflected in utility estimates	

Key: Model driver  Unknown impact;  Small/moderate impact 

Berotralstat (Orladeyo, BioCryst Pharmaceuticals)

Mechanism of action	Berotralstat is a small-molecule inhibitor of plasma kallikrein – a precursor of bradykinin.
Marketing authorisation	Indicated for routine prevention of recurrent attacks of hereditary angioedema in adult and adolescent patients aged 12 years and older.
Administration	Orally, 150 mg once daily.
List price	[redacted] per pack of 28 capsules or [redacted] per annum). The company has a patient access scheme (PAS). With **updated PAS** the annual cost is ~[redacted].

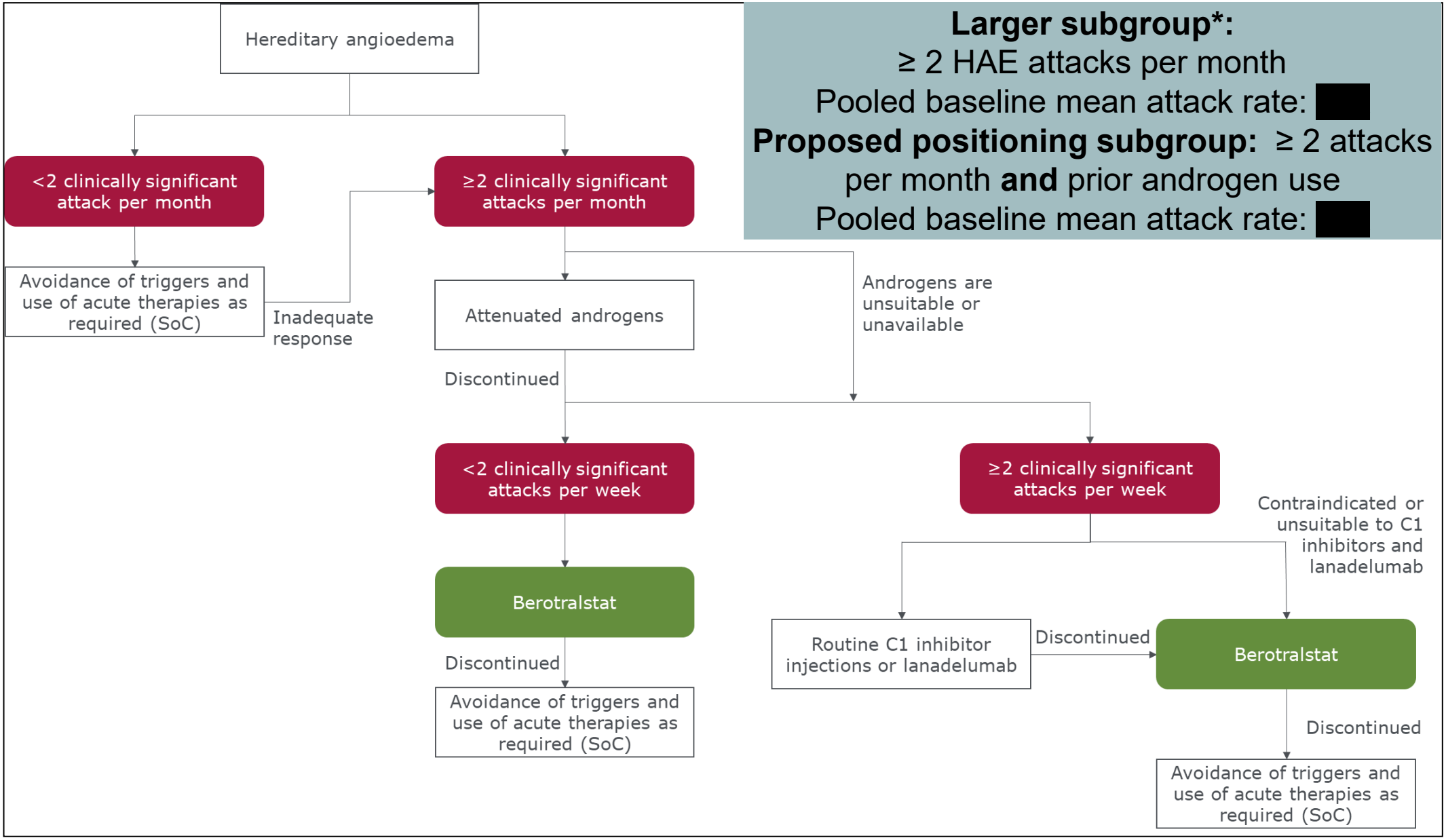
Berotralstat was granted Early Access to Medicines Scheme (EAMS) status

- EAMS 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.

APeX-2 trial

Population	People ≥ 12 years with type I or II HAE and at least 2 attacks in last 2 months.								
Intervention	Berotralstat 150mg n=40								
Comparator	Standard care (SoC) n=41 Defined as treatment on demand for acute attacks.								
Key results (Mean attacks per month)	Mo.	0	1	2	3	4	5	6	% reduction - berotralstat vs placebo
	BERO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-44.2%
	SoC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Model	• Continuation rule: people with ≥ 50% reduction in attack rate after 3 months versus baseline continue to receive berotralstat.								

Treatment pathway – Updated†



Source: updated treatment pathway from ID1624 berotralstat BioCryst ACD consultation comments v3.0

* APeX-2 intention to treat (ITT) population included people who had at least 2 attacks in the last 2 months.

† Factual inaccuracy in treatment pathway corrected post appraisal committee meeting 1 (ACM1).

Key ACD considerations

Issue	Committee's considerations
Sample size and positioning	Appropriate to consider analyses from both subgroup who have used androgens and the larger subgroup who may have not.
Extrapolation of attack rates	Uncertainty remains about attack rate reduction with berotralstat compared with standard care beyond the trial follow up period.
Health-related quality of life	• Additional analysis using utility values that reflect attack severity as well as attack rate reduction would be preferable. • It is not appropriate to include health-related quality of life effects for carers in the base case.
Continuation rule	Continuation rule may not be appropriate in clinical practice.

ACD preliminary recommendation

Berotralstat is not recommended for preventing recurrent attacks of hereditary angioedema in people 12 years and older

All cost-effectiveness estimates were **highly uncertain**. The ICERs were substantially higher than £20,000 per QALY gained, in some clinically plausible scenarios.

Committee preferred assumptions:

1. No carer disutility.
2. Treatment-arm specific costs for managing acute attacks taken directly from APeX-2.

Remaining areas of uncertainty:

1. Small patient numbers in APeX-2 is exacerbated by the company's positioning and the continuation rule.
2. Attack rate reduction with berotralstat compared with standard care beyond the trial follow up.
3. Acceptability of continuation rule in clinical practice.
4. Attack severity is not reflected in the utility estimate.

Appraisal Consultation Document (ACD) – Consultation comments

- Company
- 1x comparator company
- 2x HAE UK
- British Society of Allergy and Clinical Immunology
- United Kingdom Primary Immunodeficiency Network
- 2x other (web comments)

Themes from ACD consultation comments

Sources of evidence	Others (web comments)
	• Appropriate clinical trial evidence has been considered. • APeX-2 trial provides longer follow-up than other trials for HAE ➔ 48 weeks in APeX-2 versus 26 weeks in HELP study for lanadelumab. • Real world evidence has been accumulating through EAMS for berotralstat. Approximately 100 patients in the UK ➔ data collected through the UK HAE network.

Positioning	Patient groups	Others (web comments)
	• Positioning allows prophylaxis to patients who do not currently qualify for injectable prophylactic treatment.	• Considerable number of patients have no treatment choice apart from androgens. • Berotralstat only choice if androgens contraindicated or unsuitable. • “Inappropriate for androgen therapy" includes patients who are 12-18 years who can’t have androgens.

Summary of EAMS data

[redacted]

- [redacted] patients have had berotralstat as part of the EAMS program at point of data cut.

[redacted]

- Average baseline attack rate was [redacted] attacks per month in the three months prior to initiating berotralstat → pooled baseline attack rate in APeX-2 was [redacted].

[redacted]

- For [redacted] patients who have had 2 orders of berotralstat, monthly attack rate reduced by [redacted], at the point of the 2nd EAMS ➔ reduction was even greater for the [redacted] patients who had 4 orders of berotralstat.

[redacted]

- EAMS data suggests notably less use of acute therapy as time progresses.
- Consistent decline in use of acute therapy at time of 4th order of berotralstat.
- Aligns with APeX-2 findings ➔ less use of acute therapy with berotralstat.

Themes from ACD consultation comments

Attack severity	Comparator company	Professional groups	Others (web comments)
	• Reduction in the severity important, but all attacks can affect life → primary goal of treatment should be reducing total attacks. • Bork et al. (2000) highlights laryngeal attacks may be fatal in patients with frequent attacks as well as those with rare episodes of swelling.	• No suitable severity tools in widespread clinical use. • Surrogate measures like attack duration and amount of rescue medication can be used.	• APeX-2 included no. attacks requiring treatment, a surrogate for attack severity and location. • Attack severity diminishes with reduction in attack frequency.

Carer quality of life	Patient groups	Others (web comments)
	• Not just the patient who is affected, but family members who are dependent or provide care.	• Would like to see a measure of carer disutility included. • The impact on carers is both economically and socially significant ➔ appropriate to consider the impact on a family.

Company comments - positioning

ACD: Company proposes berotralstat is used after androgens, but this may prevent some people from accessing treatment.

Company comments

- Proposed positioning intended to include people who "cannot be treated with androgens because androgens are unsuitable or unavailable."
- Would apply to people aged <18 years and if androgens unavailable e.g. due to supply shortages.

ERG critique

- Agree that under 18s should be captured by the term 'unsuitable for androgens.'
- Inclusion of 'unavailability of androgens' may substantially increase the eligible population.
  - ➔ May add weight to the relevance of data from the larger subgroup.

Company comments - severity

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

Company comments

- Location and duration of attack are included as objective proxy measures of severity.
- Clinician suggests acute therapy usage also provides measure of attack severity.
- Data from APeX-2 indicates berotralstat reduces attack severity vs. placebo
  - reduction in laryngeal attacks.
  - Reduction in mean duration of attack by ~[redacted](patients switching from placebo berotralstat).
  - [redacted]reduction in attacks treated with acute therapy.
  - [redacted] fewer doses of acute therapy per month.

ERG critique

- Ad hoc analysis of laryngeal attacks does not provide conclusive evidence on comparative impact on severity.
- Data on duration of attack are not a randomised comparison, but a before and after comparison:
  - Analysis from the placebo randomised phase of APeX-2 was [redacted] with berotralstat vs [redacted] with placebo.

Company comments - severity

ACD : Analysis using utility values that reflect attack severity as well as attack rate reduction would be preferable

Company comments	ERG critique
• As attack duration is used as a proxy for severity, the utility values in part reflect both attack severity and attack rate. • Current approach is conservative and may not fully capture the value of berotralstat in reducing attack severity. • A scenario using administration disutility is applied for patients needing injectable acute therapy ➔ attempts to factor the need for acute therapies (a proxy for attack severity).	• No strong case presented to support effect on reducing attack severity. • Model adequately captures impact of berotralstat on severity through shorter duration and lower costs of attacks. • Including additional utility assumes Nordenfelt study and APeX-2 do not capture impact of severity on quality of life.

Company comments – carer quality of life

ACD : Not appropriate to include health-related quality of life for carers in base case

Company comments

- Caregivers experience considerable burden from time spent offering both physical and emotional support, as well as shared anxiety over attacks.
- Caregiver disutility applied for an average of [redacted] days per month for berotralstat and [redacted] days per month for SoC ➔ conservative approach.
- Accepts that previous HAE appraisals did not consider caregiver burden ➔ **carer disutility removed from base case.**

ERG critique

- No evidence that all attacks requiring acute treatment have a quality of life impact on caregivers.

Company comments – continuation rule

ACD: Continuation rule may not be appropriate (50% reduction at 3 months)

Company comments

- Rule targets patients who benefit most & avoids unnecessary adverse events.
- Incorporated into clinical practice in EAMS.
- Precedent for continuation rules in HAE ➔ C1-INH commissioning policy.
- NICE has recommended technologies with continuation rules in other disease areas.

ERG critique

- ERG's clinical adviser broadly supportive of the continuation rule.
- EAMS scheme and C1-INH policy do not strictly define the % reduction in attacks.

Patient groups	Professional groups	Others (web comments)
• Support stopping if inadequate response.	• Continuation rule could be implemented in practice. • Precedent for continuation rules ➔ C1-INH policy. • 50% reduction in attacks is a reasonable assumption.	• Attack frequency is a useful measure of disease control. • Stopping ineffective therapy routine for new high-cost drugs. • Committee should make clear guidance on continuation.

Company comments – subgroup data

ACD: Appropriate to consider analyses from the subgroup who have used androgens before and the larger subgroup who may have not

Company comments

- Positioning after androgens identified by clinical experts at Delphi panel as population with the highest unmet need
  - represents people most likely to be treated with berotralstat in NHS.
  - population in which berotralstat is most cost-effective.
- Included a scenario analysis with data from all patients with ≥2 attacks per month ➔ mitigate concerns over sample size .

ERG critique

- Both subgroups are relevant.
- Larger subgroup reduces uncertainty due to small numbers of proposed positioning subgroup.
- Updated wording to the positioning could add weight to the relevance of data from the larger subgroup.

Company comments – longer follow up data

96 week data shows berotralstat had a durable effect and benefit increased over time

ERG: substantial attrition in numbers informing monthly reductions

- If poor responders more likely lost to follow-up, may partly explain sustained reduction.
- unweighted averages to extrapolate reduction could generate bias ➔ scenario analysis indicate minimal impact.

  ➔ for responders, less support for a continued decline attack frequency beyond month 3.

Company comments – extrapolating SoC

- Revised extrapolations to a more conservative approach:
  - **Berotralstat:** Mean monthly attack rate from month 4 to 24 **(BERO1).**
  - **SoC:** Mean monthly attack rate is tapered linearly to pooled baseline attack rate over months 7-12 and month 12+ = baseline attack rate (**SOC 2**).

ERG

- If baseline attack rate is a true representation of average monthly attack rate, then it may be applied from the start of model.
- If reductions/variability in the placebo arm reflects regression to the mean, then carrying forward the average attack rate through months 0-6 is a relevant scenario.
- ACD suggests subtracting the average % reduction in placebo arm from berotralstat arm → similar to carrying forward the average % reduction for SoC.

  ➔ Following scenarios should be considered to address range of uncertainty

  - In conjunction with BERO1

    SOC1: month 6+ = baseline rate & **SOC3:** month 6+= average of month 1-6
  - In conjunction with SOC 1

    BERO 2 and 3: 100% and 50% of SoC average subtracted from BERO1.

Extrapolating SoC- Modelled results

Larger subgroup experiencing ≥ 2 attacks per month at baseline*

*Continuation rule applied to responders.

Cost-effectiveness results: Berotralstat PAS only[#]

- **Larger subgroup: ≥ 2 attacks per month only.**
- Pooled baseline attack rate ([redacted]).
- Unweighted percentage reduction in attacks used for extrapolation.

	% attack rate reduction extrapolation	Costs £	QALYs	Incr. costs £	Incr. QALYs	ICER (£/QALY)
SoC 1 + BERO 1	SoC: Baseline	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
	Berotralstat: Average	[redacted]	[redacted]	[redacted]	[redacted]	
SoC 2 + BERO 1	SoC: Tapered to baseline	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
	Berotralstat: Average	[redacted]	[redacted]	[redacted]	[redacted]	
SoC 3 + BERO 1	SoC: Average	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat: Average	[redacted]	[redacted]	[redacted]	[redacted]	
SoC 1 + BERO 3	SoC: Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Berotralstat: Average minus 100% placebo effect	[redacted]	[redacted]	[redacted]	[redacted]	
SoC 1 + BERO 2	SoC: Baseline	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
	Berotralstat: Average minus 50% placebo effect	[redacted]	[redacted]	[redacted]	[redacted]	

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

Cost-effectiveness results: Berotralstat PAS only[#]

- **Company positioning subgroup: ≥ 2 attacks per month and prior androgen use.**
- Pooled baseline attack rate ([redacted]).
- Unweighted percentage reduction in attacks used for extrapolation.

	% attack rate reduction extrapolation	Costs £	QALYs	Incr. costs £	Incr. QALYs	ICER (£/QALY)
SoC 1 + BERO 1	SoC: Baseline	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
	Berotralstat: Average	[redacted]	[redacted]	[redacted]	[redacted]	
SoC 2 + BERO 1	SoC: Tapered to baseline	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
	Berotralstat: Average	[redacted]	[redacted]	[redacted]	[redacted]	
SoC 3 + BERO 1	SoC: Average	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
	Berotralstat: Average	[redacted]	[redacted]	[redacted]	[redacted]	
SoC 1 + BERO 3	SoC: Baseline	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
	Berotralstat: Average minus 100% placebo effect	[redacted]	[redacted]	[redacted]	[redacted]	
SoC 1 + BERO 2	SoC: Baseline	[redacted]	[redacted]	[redacted]	[redacted]	Berotralstat dominant
	Berotralstat: Average minus 50% placebo effect	[redacted]	[redacted]	[redacted]	[redacted]	

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

☐ Company's base case

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Company comments – uncaptured benefits

Company:

- Model excludes any potential benefits of berotralstat's mode of administration ➔ provided a scenario in which administration disutilities are applied for attacks requiring acute therapy using data from Holko et al (2018).

ERG:

- Assumes Nordenfelt study does not capture the quality of life impact of treating attacks with injectables.
- -0.147 utility decrement applied in this scenario analysis compared to the 0.024 utility increment applied to the lanadelumab arm of TA606.

Company:

- Carer quality of life not included in base case.
- Scenario including caregiver effects increases incremental QALY gain by [redacted] in company base case.