Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over

For committee – contains [redacted] information

Technology appraisal committee C [11 June 2025]

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Company: CSL Behring

Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

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Background on hereditary angioedema (HAE)

Rare genetic disorder, associated with uncontrolled inflammation

Epidemiology

- Rare, estimated 1,041 people live with HAE in England and Wales. Usually present in childhood, with mean age of onset between 8 and 12 years
    - In Appendix: Anticipated eligible population size for garadacimab

Symptoms

- Chronic genetic disorder of uncontrolled inflammation, characterised by recurrent and unpredictable attacks of swelling of the skin or submucosal tissues
- HAE attacks are unpredictable. Can be associated with trauma, emotional stress, menstruation, infections, or some medications. Often, the trigger is not identified

Subtypes

- HAE can be categorised into clinically indistinguishable subtypes
- Most cases caused by mutation affecting C1 esterase inhibitor (C1-INH) gene: **Type I** (85%), **Type II** (15%). HAE with normal C1-INH uncommon subtype (<1%)

Abbreviations: C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema

Patient perspectives

Attacks are debilitating. Unmet need for access to appropriate medication

About having an HAE attack, from Hereditary Angioedema UK

- Attacks are large, very painful swellings of subcutaneous tissues anywhere in body – uncomfortable and unsightly, can be fatal (e.g. laryngeal swelling)
- Debilitating with rapid onset over a few hours. Home-injected medication starts to work quickly but swellings take 2 to 3 days (up to 1 week) to go. After an attack, feel drained with flu-like symptoms and extreme fatigue
- People can be attack free if well managed, but many can't access appropriate medication

Expected advantages of garadacimab

- Easily transportable treatment and no need for constant refrigeration
- Anxiety is major trigger for an attack. Garadacimab would reduce anxiety allowing people to travel with small and portable device
- One stop medication to administer for any HAE attack

Swollen hands… Swollen feet… [make parts of everyday life impossible]… Swollen abdomen leads to intense, excruciating pain

A child having an attack quickly becomes agitated, in pain …and swellings. Needs to be treated… quickly… (usually IV treatment in hospital)

[New treatment options]… will be good for patients…Effective prophylaxis is most important aspect in the development of HAE treatment

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Abbreviations: HAE, hereditary angioedema; IV, intravenous

Clinical perspectives

Strict access criteria for current treatments, which limits options for some patients

Consideration of current treatment, from BSI and RCP

- Care of patients is through NHSE specialist immunology and allergy clinics
- Access to treatment defined by NHSE commissioning policies and NICE TAs
- Criteria based only on attack frequency disadvantage children and young people, who often have fewer attacks than adults, but can still be significantly affected – school absence and lower educational attainment
- HAE mortality relatively low due to on-demand therapies

Potential benefits of garadacimab

- Highly effective long-term prophylactic (preventative) treatment given as SC injection every 4 weeks. Different drug target than existing medicines and less frequent administration than lanadelumab (can be every 2 weeks)
- For patients with <2 attacks per week, garadacimab expected to provide more clinically meaningful benefits than current treatment options

≥2 attacks per week on oral medication: patients already have access to the most effective licensed treatments

Unmet need in patients with ≥2 attacks per month but <2 per week. If attack frequency not reduced by 50% on berotralstat, there are limited options

<2 attacks per month: patients have no access to effective, licensed prophylactic treatments

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Abbreviations: BSI, British Society for Immunology; HAE, hereditary angioedema; NHSE, NHS England; RCP, The Royal College of Pathologists; SC, subcutaneous; TA, technology appraisal

Equality considerations

Access to current treatments may be limited by patient age and religious beliefs

Potential equality issue raised		Related considerations
Age	1. Access to treatment is based on age (BSI, RCP, NHSE) 2. Access criteria based on attack frequency can disadvantage children and young people because they may have attack frequencies below current access criteria • Children and young people are significantly affected by HAE despite have fewer attacks than adults • Impact on children can include missed school days → impacts education attainment effects (uncaptured)	• NICE committee makes recommendations within a technology's marketing authorisation • Garadacimab is indicated for use in people aged 12 years and older • Attack frequency criteria
Religion	1. Religious groups may be unwilling to have blood product-derived treatments • C1-INH comparators (Cinryze and Berinert) are derived from human plasma	• Lanadelumab is an existing alternative to C1-INHs, which is not from human plasma • Garadacimab would be another option that is not from human plasma

Abbreviations: BSI, British Society for Immunology; C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; NHSE, NHS England; RCP, The Royal College of Pathologists

Key issues

Section	Issue (EAG report issue number)	Status*	ICER impact within EAG model	
			≥2 attacks per **month**	≥2 attacks per **week**
Decision problem	Uncertainty around treatment pathway for people with HAE (1)	**For committee discussion**	Large	N/A
Clinical effectiveness	Methods and trials used in ITC (2)	Resolved: Appendix	N/A	N/A
Cost effectiveness	Methods and data used to estimate treatment effectiveness (3)	Resolved: Appendix	N/A	N/A
	Handling of berotralstat stopping rule (4)	**For committee discussion**	Large	N/A
	Lanadelumab switching between Q2W and Q4W (5)	**For committee discussion**	N/A	Small
	Calculation of patient utilities (6)	**For committee discussion**	Large	Small

*A technical engagement (TE) step was included for this evaluation (March 2025). As a result, some aspects of company and EAG approach have been updated, including 2 Key issues being resolved – slides for these are included in Appendix but may not be discussed in the committee meeting

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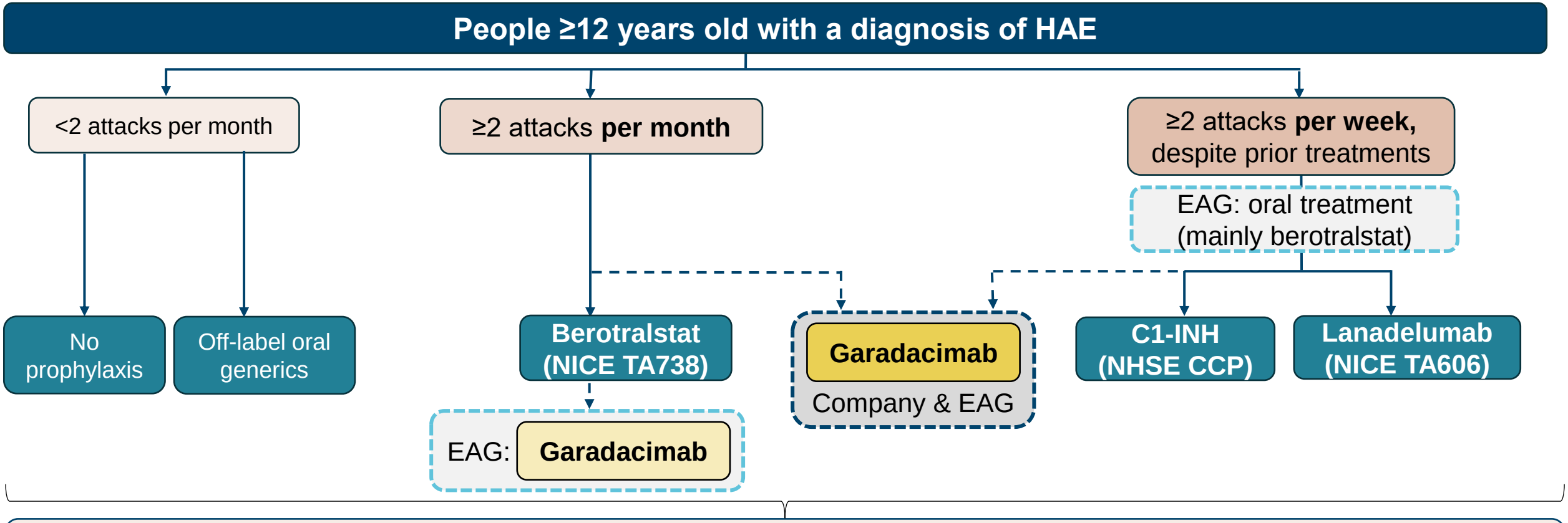
Abbreviations: HAE, hereditary angioedema; ITC, indirect treatment comparison; Q2W / Q4W, every 2 / 4 weeks

Treatment pathway for long-term prophylaxis



On-demand: C1-INHs or icatibant as adjunctive treatments for acute attacks irrespective of attack frequency or concurrent use of LTP options. **Pre-procedure prophylaxis:** C1-INHs used before having dental, medical, obstetric or surgical procedures

Is the company's proposed positioning of garadacimab as an alternative alongside berotralstat without considering line of use in the ≥2 attacks per month population reasonable?

Abbreviations: C1-INH, C1-esterase inhibitor; CCP, clinical commissioning policy; EAG, expert assessment group; HAE, hereditary angioedema; LTP, long-term prophylaxis; NHSE, NHS England

Garadacimab (Andembry, CSL Behring)

Marketing authorisation	• Indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older (granted January 2025)
Mechanism of action	• Fully human, recombinant immunoglobulin G4 (IgG4)/lambda monoclonal antibody and specific inhibitor of activated Factor XII (FXIIa) • Inhibition of FXIIa blocks cascade of events leading to an HAE attack
Storage	• Refrigerator. May be at room temperature (≤25°C) for a single period of up to 2 months
Administration	• Subcutaneous (SC) injection by pre-filled pen (single use autoinjector device) • Initial loading dose of 400 mg administered as 2 x 200 mg injections on Day 1, followed by a monthly injected dose of 200 mg
Price	• List price of [redacted] per unit (1 pre-filled pen of 200 mg) • List price cost of treatment in 1st year including initial loading dose is [redacted], followed by an annual cost of [redacted] thereafter (including VAT) • Patient access scheme is applicable

Abbreviations: Factor XII; FXIIa, activated Factor XII; HAE, hereditary angioedema; IgG4; immunoglobulin G4; SC, subcutaneous

Key issue 1: Uncertainty around treatment pathway for HAE (1/2)

Company disagrees with EAG's 2nd-line scenario in ≥2 attacks per month population

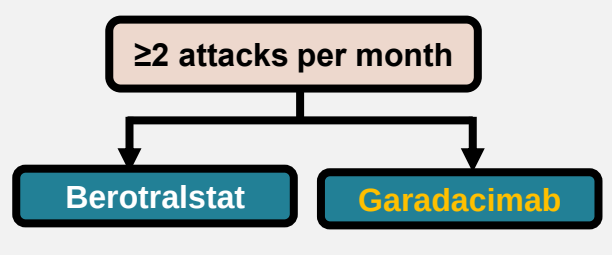
NHSE Specialised Immunology and Allergy Clinical Reference Group

- Company's proposals consistent with clinical commissioning algorithm and accurately reflect current treatment landscape and exclusions for anti-fibrinolytics and attenuated androgens, which are not SoC

HAE attack frequency: ≥2 attacks per **month:**

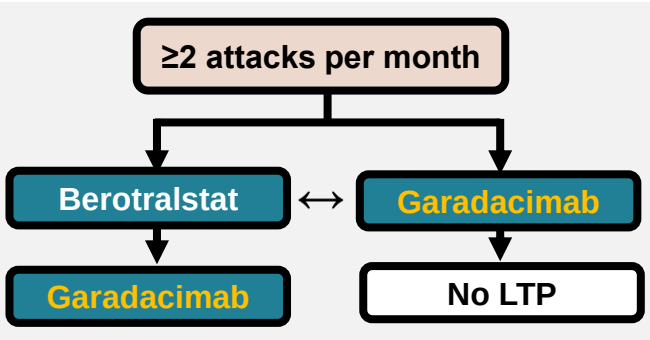
Company – approach unchanged after TE

- ≥2 attacks per month population supported by NHSE algorithm
  - Improves treatment choice – see HAE expert views and feedback
- Disagrees with EAG's approach:
  - People having garadacimab first-line can't have berotralstat second-line
  - Comparing garadacimab with no LTP at second-line outside NICE scope



EAG comments – approach unchanged after TE

- Unmet need for LTP options when <2 attacks per week
- EAG explores scenario for ≥2 attacks per month population for garadacimab second-line after berotralstat, assuming same efficacy as first-line
  - Proposed options for garadacimab positioning sit within NHSE pathway



Abbreviations: LTP, long-term prophylaxis; SoC, standard of care

Key issue 1: Uncertainty around treatment pathway for HAE (2/2)

Company disagrees with EAG's 2nd-line scenario in ≥2 attacks per month population

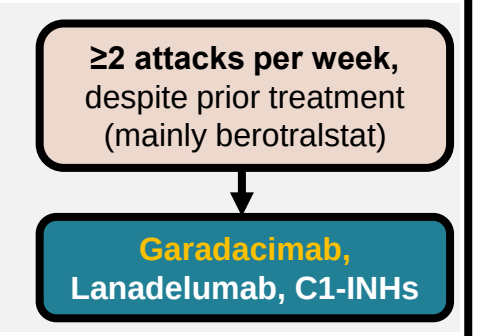
EAG comments continued

- EAG's clinical expert advice – treatment switching permitted, so people can have berotralstat after first trying garadacimab
- Uncertainty remains around effectiveness of different sequences of treatments in HAE
- Berotralstat cost-effective compared to BSC (no prophylaxis) in TA738. Requested company provide analysis versus BSC, to support 1st line comparison of garadacimab versus berotralstat where there is uncertainty about berotralstat stopping rule (see Key issue 4)
  - BSC comparison not done by company – EAG provided cost-effectiveness results vs BSC

HAE attack frequency: ≥2 attacks per **week:**

EAG comments

- Lanadelumab optimised recommendation by attack frequency to ≥2 attacks per week population (high efficacy / high cost)
- **Garadacmib cost-effective versus lanadelumab (dominates)** in company and EAG base case, so ≥2 attack per week population a less important consideration



Which approach does the committee prefer? Is consideration of garadacimab as a first- or second-line option after berotralstat reasonable in people having ≥2 HAE attacks per **month**?

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Abbreviations: BSC, best supportive care; C1-INH, C1-esterase inhibitor; EAG, evidence assessment group; HAE, hereditary angioedema; TE, technical engagement

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Key clinical trials

Table: Phase 3 clinical trial designs and outcomes

	VANGUARD (CSL312_3001)	OLE study (CSL312_3002)
Design	Phase 3 double-blind, RCT	Phase 3b open-label study
Population	Aged ≥12 years HAE-1 or HAE-2: ≥3 attacks in 3 months before screening	Aged ≥12 years HAE-1 or HAE-2: ≥3 attacks in 3 months before screening
Intervention	Garadacimab 200 mg SC, Q4W (n=39)	Garadacimab 200 mg SC, Q4W (n=161)
Comparator	Placebo SC Q4W (n=25)	[none]
Duration	6 months	At least 12 months (ongoing)
Primary outcome	Time-normalised number of HAE attacks, 6-month treatment period	TEAE
Secondary outcomes	% reduction in monthly number of HAE attacks Number of people attack-free	Time-normalised number of HAE attacks, per month and year
Locations	7 countries, not UK	14 countries, not UK
Used in model	Time-normalised number of HAE attacks; number of HAE attacks requiring on-demand or acute treatment; % of people attack-free; adverse events	Adverse events

Abbreviations: OLE, open-label extension; SC, subcutaneous; TEAE, treatment-emergent adverse events

Appendix: Baseline characteristics

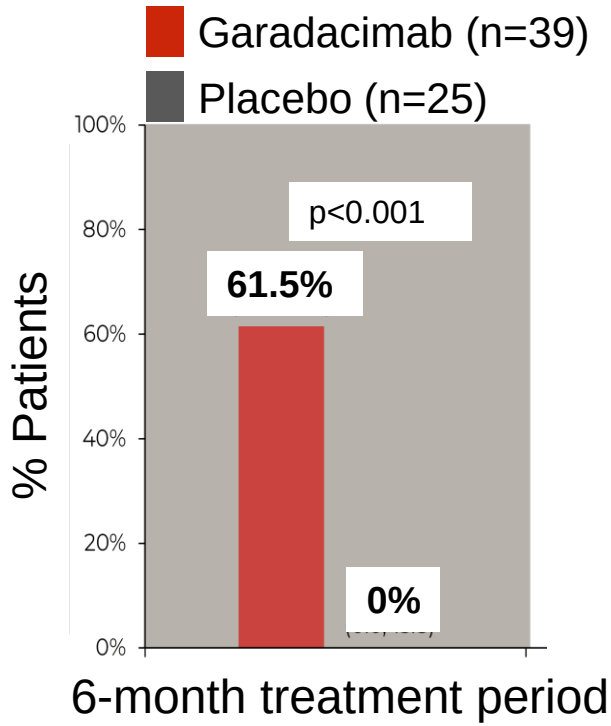
Clinical trial results

Garadacimab reduces number HAE attacks over 6 months trial period vs placebo

Table: Efficacy results of VANGUARD trial

ITT population: people who had ≥1 attack per month over 6-month treatment period	Garadacimab (n=39)	Placebo (n=24)
Baseline mean HAE attacks per month, n	3.07	2.52
Mean **number of HAE attacks** per month, n	0.27	2.01
• Difference in means, %	−86.5%; p<0.001	
Mean **reduction in monthly HAE attacks** in treatment period vs run-in, %	90.7%	20.2%
• Difference	p<0.001	
Proportions of patients **attack free**, %	61.5%	0%
• Difference	p<0.001	
Number of HAE attacks **needing on-demand treatment** per month, n	0.23	1.86
• Difference in means, %	−87.5%; p<0.001	

Figure: Proportion of patients attack free in VANGUARD trial (ITT)



Company: Efficacy is consistent across different time on treatment, prior exposure to treatment and baseline attack frequency. Effects maintained in longer term – Appendix

EAG: Not a trial of 1st line treatment. Participants needed to have ≥3 HAE attacks during 3 months before screening → not specified in NICE scope

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; ITT, intent-to-treat; n, number

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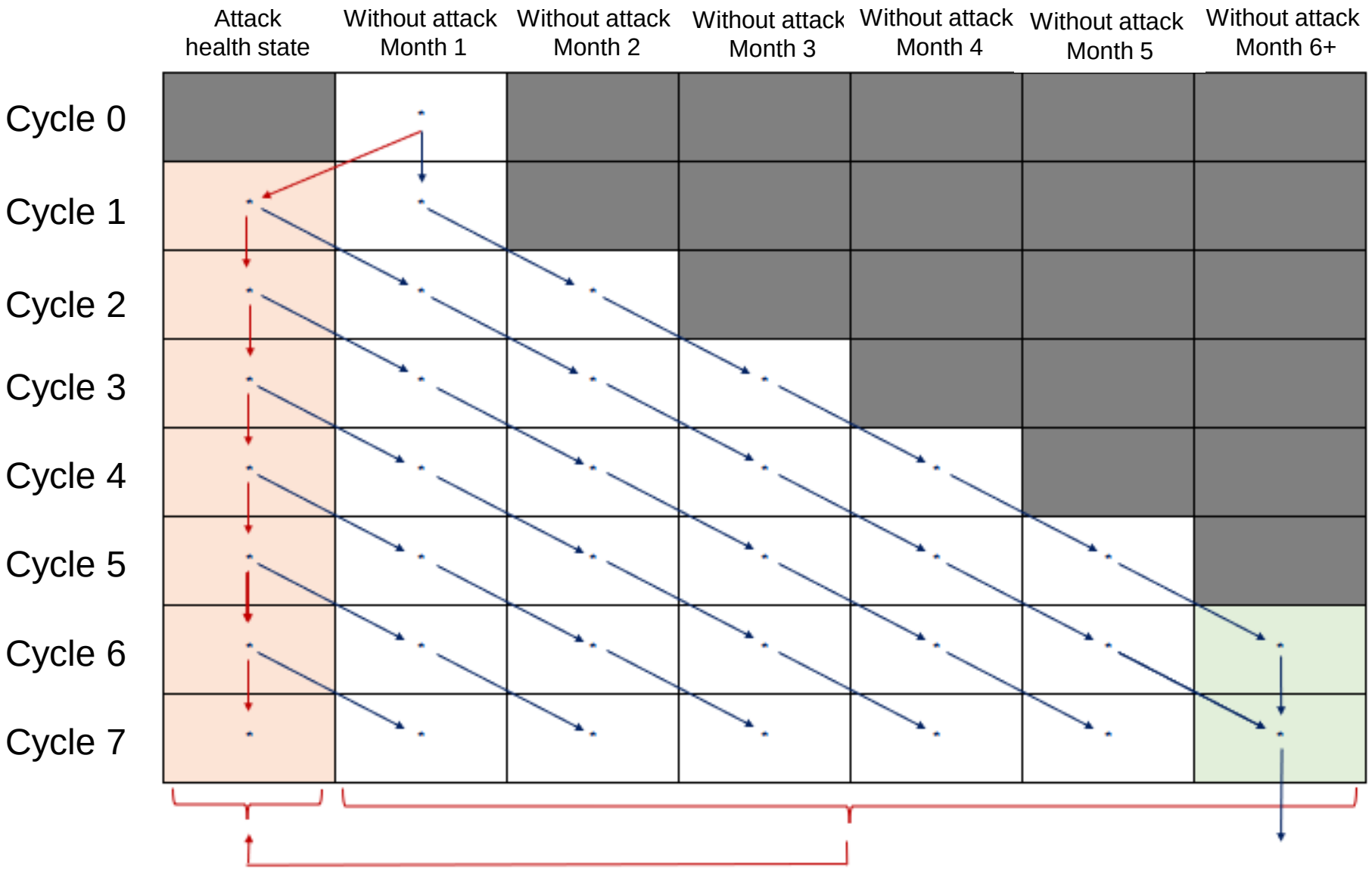
Company's model overview (1/2)



Key:
- Attack health state
- Without attack health state
- Ultimate without attack health state

Company:

Cohort-based Markov model:

- 1 cycle = 28 days
- No half-cycle correction
- Lifetime horizon (60 years)
- Severe HAE attack and laryngeal attack modelled separately due to resource costs differences

3 primary health states with 6 tunnel states, which house people who have not had an attack in successive cycles and track amount of time since previous HAE attack

Note: Transition to attack state can occur from any cycle ( )

Abbreviations: HAE, hereditary angioedema; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Company's model overview (2/2)

- Technology affects **costs** by:
  - Changing costs of long-term prophylaxis relative to comparator treatments
  - Reducing costs of treating acute attacks, both in terms of drug costs and health-care resource use
- Technology affects **QALYs** by:
  - Reducing number of HAE attacks, which has direct impact on QoL of patients (key driver) and carers
  - Increasing time spent attack-free: patients assumed to return to general population QoL after 6 months being attack free
  - Reducing severity of attacks relative to most comparators – based on a naïve comparison of data from a variety of sources which used varying descriptions of severity
- **Assumptions with greatest ICER effect include:**
  - Population (≥2 attacks per month or ≥2 attacks per week) and relevant comparator
  - Duration applied to QoL impacts for each HAE attack

EAG:

- Company added tunnel states based on expert option
- These capture improvements in QoL and associated resource use
- Addition of tunnel states is main difference between this model and previous ones appraised by NICE in HAE (TA606 and TA738)
- Company and EAG's clinical advisors stated that they would not expect patient QoL to fully return to that of general population (as model assumed after 6 months being attack free)

Abbreviations: HAE, hereditary angioedema; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal

How company incorporated evidence into model

Table: Key assumptions and evidence sources in company's base case model – after TE

Input	Assumption and evidence source
Baseline inputs	VANGUARD trial
Garadacimab treatment effect	ITC – fixed effect NMA excluding garadacimab phase 2 trial
Clinical evidence inputs	HAE attack rate, survival analysis and time to first attack, time normalised number of HAE attacks from VANGUARD trial
Treatment waning effect	Lifetime
Adverse event rates	VANGUARD trial and open label extension
Mortality	Disease-specific mortality not considered
Patient utility	'Attack' and 'attack free' utilities were based on EQ-5D-5L data from Nordenfelt et al. (2014). Uses 6 tunnel states
Caregiver utility	Informed by Lo et al. (2022)

Key issue 4: Handling of berotralstat stopping rule (1/3)

Company updated approach uses recent limited study data on berotralstat

Background

- TA738: berotralstat is stopped in non-responders (if attack frequency not reduced by ≥50% after 3 months)
- Berotralstat stopping rule not implemented in trial (pre-TA738), so no trial data specifically in responders
- Data on responders was **redacted** in TA738 guidance, so could not be used by company in current topic. NICE asked TA738 company if data could be made publicly available but they did not agree to this

Company

- Up to month 3: NMA for berotralstat efficacy data → appropriate to include responders & non-responders
- After month 3: No data from trial or TA738 on which to base assumptions about berotralstat responders

Base case	Methods and data used for responder assumptions after month 3
Original submission	Extrapolated NMA data as average attack rate carried forward up to month 3 to those staying on berotralstat after month 3 (responders & non-responders) → efficacy underestimated
After TE	Used Elbashir et al. (2024) poster: ~[redacted] of study participants could continue berotralstat and average attack rate in these at month 12–24 was applied to responders in model

- Acknowledged limitations of Elbashir et al. **poster evidence**, including limited description of methods, but considered it represents best available source to model efficacy of berotralstat responders
- Lack of evidence for EAG's base case, which is based on clinical expert opinion and lanadelumab data

Key issue 4: Handling of berotralstat stopping rule (2/3)

Modelled attack rate for berotralstat differs depending on approach used

EAG comments

- Understood difficulty company faced having no data on 'responders' from berotralstat trial or TA738
- EAG's preferred approach was to assume from month 3, berotralstat efficacy was same as lanadelumab Q2W, which was based on clinical advice to EAG that berotralstat responders can do very well

Elbashir:

- Considered problems with using this source were too great for it to be used in EAG base case
- Disagreed with company's interpretation (see next slide), so is used differently in EAG scenario
- EAG's implementation was more favourable to berotralstat

EAG base case:

- Applied attack rate reduction of lanadelumab to berotralstat
- EAG base case gave lowest attack rate of the different methods

Table: Comparison of modelled attack rate in berotralstat arm when using different methods

Month	EAG base case	EAG scenario use of Elbashir	Company base case use of Elbashir
3	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
25+	[redacted]	[redacted]	[redacted]

Abbreviations: ITC. Indirect treatment comparison; NMA, network meta-analysis

≥2 attacks per **month** | Large impact

Key issue 4: Handling of berotralstat stopping rule (3/3)

EAG prefers to use efficacy of lanadelumab as proxy for berotralstat responders

EAG comments continued

Elbashir	EAG comments
Suitability	[redacted] of participants began treatment before stopping rule introduced (Oct. 2021) • Did not discontinue due to lack of response → underestimates berotralstat efficacy • Discontinuations occurred for mixed reasons (stopping rule and other reasons)
Implementation	**Methods for using data** (flow chart in Appendix)**:** Including that company assumed Figure 2 in Appendix included people who had not discontinued berotralstat (completers), but EAG considered it was standard ITT analysis. Also, potential maths error noted **Assumptions:** In calculating proportionate reduction in attack rate for different subgroups compared to baseline, company assumed baseline values were same for both groups **Attack rate ratio NMA disregarded:** naïve comparison → not in line with NICE guidance

- EAG's base case and scenarios used NMA data for attack rate in month 3, then used different assumptions to make adjustments to the attack rates in subsequent months
- Given uncertainty, analysis of berotralstat versus BSC (as in TA738) could further support first-line comparison of garadacimab versus berotralstat → triangulation of results versus berotralstat
- Large ICER impact: company = best case, EAG preferred = worst case; EAG Elbashir scenario in between

Question for clinical experts: is it reasonable to assume that responders to berotralstat have similar efficacy to people having lanadelumab (EAG approach)? Which approach does the committee consider is most reasonable to account for unavailable data on berotralstat response and stopping?

Abbreviations: ITC. Indirect treatment comparison; NMA, network meta-analysis

Key issue 5: Lanadelumab switching between Q2W and Q4W (1/2)

Some differences in way company and EAG model lanadelumab dosing switch

Background

- Lanadelumab: starting dose 300mg Q2W, dose reduction to 300mg Q4W in people stable and attack-free, especially those with low weight. TA606: assumed 77% patients had Q4W dosing after year 1 (trial)
- **Issue has minor impact on cost-effectiveness due to garadacimab being dominant vs. lanadelumab**

NHSE Specialised Immunology and Allergy Clinical Reference Group:

- Efficacy of lanadelumab and switching from Q2W to Q4W likely overestimated in TA606
- RWE sources from outside UK do not appear more valid than UK real world data (Dorr et al.) since threshold for commissioning in Europe based on EMA licence, which has no starting threshold of ≥2 attacks per **week** (unlike UK) → skews ability to reduce to Q4W due differences in comparators and assumptions

Company

- UK RWE shows 45% of patients are on Q4W dosing by end of 1st year of treatment (n=60; Dorr et al. 2022)
- Clinical expert advice was there is a difference in efficacy between lanadelumab Q2W and Q4W

EAG comments:

- Disagrees with company that switching is gradual and assumption of efficacy for Q4W dosing
- Clinical advisers to EAG suggested faster switch more common (≤1 year) and proposed larger EU RWE study (Magerl et al.), which compared efficacy of Q2W and Q4W dosing on attack-free rates

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Abbreviations: Q2/4W, every 2 or 4 weeks; RWE, real work evidence; SmPC, summary of product characteristics; TE, technical engagement

Key issue 5: Lanadelumab switching between Q2W and Q4W (2/2)

Some differences in way company and EAG model lanadelumab dosing switch

EAG comments:

Table: Comparison of company and EAG model assumptions after TE

Assumption	Company	EAG preferred
Proportion	45% switch to Q4W	45% switch to Q4W
Timing of switch to Q4W	Linear split across cycles • Over 12-month period	Instantaneous at 12th cycle • At 12 months (based on Magerl RWE)
Efficacy of Q4W dosing	**= people starting on Q4W in HELP trial** • 3 arm trial of lanadelumab Q2W / lanadelumab Q4W / placebo does not reflect switching in practice	**= same as Q2W dosing in model** • Reasonable assumptions for stably attack-free patients

- **Company's approach underestimates lanadelumab efficacy:** by assuming switching is gradual, and starts earlier, benefits garadacimab when it is assumed that patients on lanadelumab Q4W do not achieve same level of response that they had on Q2W in model

Questions for clinical experts: is the company assumption of a linear rate of switching up to 12 months, reasonable? Is the efficacy of lanadelumab different between Q2W to Q4W dosing among people treated in UK clinical practice who would have Q4W dosing?

Abbreviations: Q2/4W, every 2 or 4 weeks; RWE, real work evidence; SmPC, summary of product characteristics; TE, technical engagement

Key issue 6: Calculation of patient utilities (1/2)

Differences in company and EAG model patient utilities

Table: Comparison of company and EAG modelled utility for an average 41-year-old patient 1-year post baseline, by treatment

	≥2 attacks per **month**		≥2 attacks per **week**	
Treatment	**Company** (3.13-day attacks)	**EAG** ([redacted]-day attacks)	**Company** (3.13-day attacks)	**EAG** ([redacted]-day attacks)
Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab	[redacted]	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]	[redacted]
Berinert	[redacted]	[redacted]	[redacted]	[redacted]
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]

Company

Table: Utility value ranges, by number of attacks in past 6 months

Attacks over 6 months, n	Utilities: Banerji et al EQ-5D mappings*
0	0.89 – 0.96
1-3	0.83 – 0.93
4-6	0.77 – 0.88
7-12	0.74 – 0.86
≥13	0.64 – 0.79

*US survey of 445 patients (2017), 68.5% receiving LTP (mostly C1-INHs). Utilities mapped from SF-12

EAG comments: ***Banerji et al (2020) utility mapping not accepted as relevant to considering impact of time spent attack free 'attack free', but could be used as an alternative source to Nordenfelt to model quality of life

Abbreviations: AEs, adverse events; HRQoL, health-related quality of life

Key issue 6: Calculation of patient utilities (2/2)

Some differences in way company and EAG model patient utilities

Company

- **Applies disutility** in model for HAE attacks based on Nordenfelt et al. 2014 (in line with previous appraisals)
- Incorporates **time spent attack-free** to increase HRQoL, based on clinical expert opinion that patients experience increasing utility the more successive cycles they spend without an attack
- Assumes **impact of attack continued after attack ended**

Table: Attack disutility estimates

HAE attack severity	Disutility
Mild	0.07
Moderate	0.369
Severe or laryngeal	0.486

EAG comments

- Notes inconsistencies with past appraisals using same source, in way decrements calculated and applied
- Nordenfelt source for utilities is 15 years old with limited description of methods
  - Appendix: Summary of differences in implementation of Nordenfelt utilities
- Company's 3.13-day impact of attack is longer than actual attack duration and is based on Lumry 2010, for average number of days of work or leisure missed per attack → inflates impact of attack on HRQoL
- EAG did not see sufficient evidence to change from attack duration in VANGUARD trial ([redacted] days), but explored longer durations in scenarios → key ICER driver, greatest effect in ≥2 attacks per month population

Which approach does the committee prefer? Does the impact of an attack last longer than its duration? Which utility values most accurately reflect the impact of HAE attacks on patient health-related quality of life?

Abbreviations: EAG, evidence assessment group; HAE, hereditary angioedema; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio

Summary of differences between company and EAG base cases

Table: Differences in assumptions between company and EAG base cases – after TE

Assumption	Company base case	EAG base case
Population(s)	≥2 HAE attacks per month	≥2 HAE attacks per month ≥2 HAE attacks per week
Berotralstat stopping rule	~[redacted] participants continue berotralstat Average attack rate in these at month 12–24 applied to responders	From month 3 berotralstat efficacy same as lanadelumab Q2W
Lanadelumab switch between Q2W and Q4W dosing	45% switch, gradually over 12 months Efficacy = people starting on Q4W in HELP trial	45% switch, instantly at 12 months Efficacy = same as Q2W dosing in model
Patient utility values	Uses Nordenfelt, but • Impact of attack = longer than duration of attack • Incorporates time spent attack free (using 6 tunnel states)	Based on Nordenfelt • Impact of attack = duration of attack (in trial) • Utility is only a function of time spent attack free based on number of previous attacks
Caregiver disutility (summary in Appendix)	• Lo et al 2022: disutility of 0.145 per qualifying HAE attack • 1.46 caregivers per household	• Pennington et al 2024: disutility of 0.0123 for every 0.1 patient disutility per qualifying HAE attack • 1 caregiver per household

Summary of cost-effectiveness results

Large difference between company and EAG base case results in ≥2 attacks per month population, but both were cost-effective in ≥2 attacks per week population

≥2 HAE attacks per month population (including garadacimab PAS and cPAS):

- **Company base case** ICER for garadacimab versus berotralstat at higher end of range normally considered a cost-effective use of NHS resources (£20,000 to £30,000/QALY gained)
- **EAG base case** ICER for garadacimab versus berotralstat substantially higher than £30,000/QALY

≥2 HAE attacks per week population (including garadacimab PAS and cPAS):

- Garadacimab dominated in company and EAG base cases – it was less costly and more effective than lanadelumab and C1-INHs

Further details of cost-effectiveness results will be presented in part 2. Note:

- QALY weighting for **severity** does not apply – see Appendix
- Company has not made a managed access proposal for garadacimab

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Abbreviations: cPAS, confidential patient access scheme; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years

Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Summary**

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Key issues

Section	Issue (EAG report issue number)	Status*	ICER impact within EAG model	
			≥2 attacks per **month**	≥2 attacks per **week**
Decision problem	Uncertainty around treatment pathway for people with HAE (1)	For committee discussion	Large	N/A
Clinical effectiveness	Methods and trials used in ITC (2)	Resolved	N/A	N/A
Cost effectiveness	Methods and data used to estimate treatment effectiveness (3)	Resolved	N/A	N/A
	Handling of berotralstat stopping rule (4)	For committee discussion	Large	N/A
	Lanadelumab switching between Q2W and Q4W (5)	For committee discussion	N/A	Small
	Calculation of patient utilities (6)	For committee discussion	Large	Small

Abbreviations: HAE, hereditary angioedema; ITC, indirect treatment comparison; Q2W / Q4W, every 2 / 4 weeks

Key questions for committee

Section	Key questions
Decision problem	Is the company's proposed positioning of garadacimab as an alternative alongside berotralstat without considering line of use in the ≥2 attacks per month population reasonable?
	Should the cost-effectiveness analysis be based on attack frequency (EAG)? Is consideration of garadacimab as just a first-line option alongside berotralstat reasonable in people having ≥2 HAE attacks per month?
Cost effectiveness evidence	Is it reasonable to assume that responders to berotralstat have similar efficacy to people having lanadelumab (EAG approach)? Which approach does the committee consider is most reasonable to account for unavailable data on berotralstat response and stopping?
	Is the company assumption of a linear rate of switching up to 12 months, reasonable? Is the efficacy of lanadelumab different between Q2W to Q4W dosing among people treated in UK clinical practice who would have Q4W dosing?
	Does the impact of an attack last longer than its duration? Which utility values most accurately reflect the impact of HAE attacks on patient health-related quality of life?

Abbreviations: HAE, hereditary angioedema; ITC, indirect treatment comparison; Q2W / Q4W, every 2 / 4 weeks

Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over

Supplementary appendix

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Back to main deck: Background on HAE

Anticipated eligible population size for garadacimab

Eligible population size estimated by company

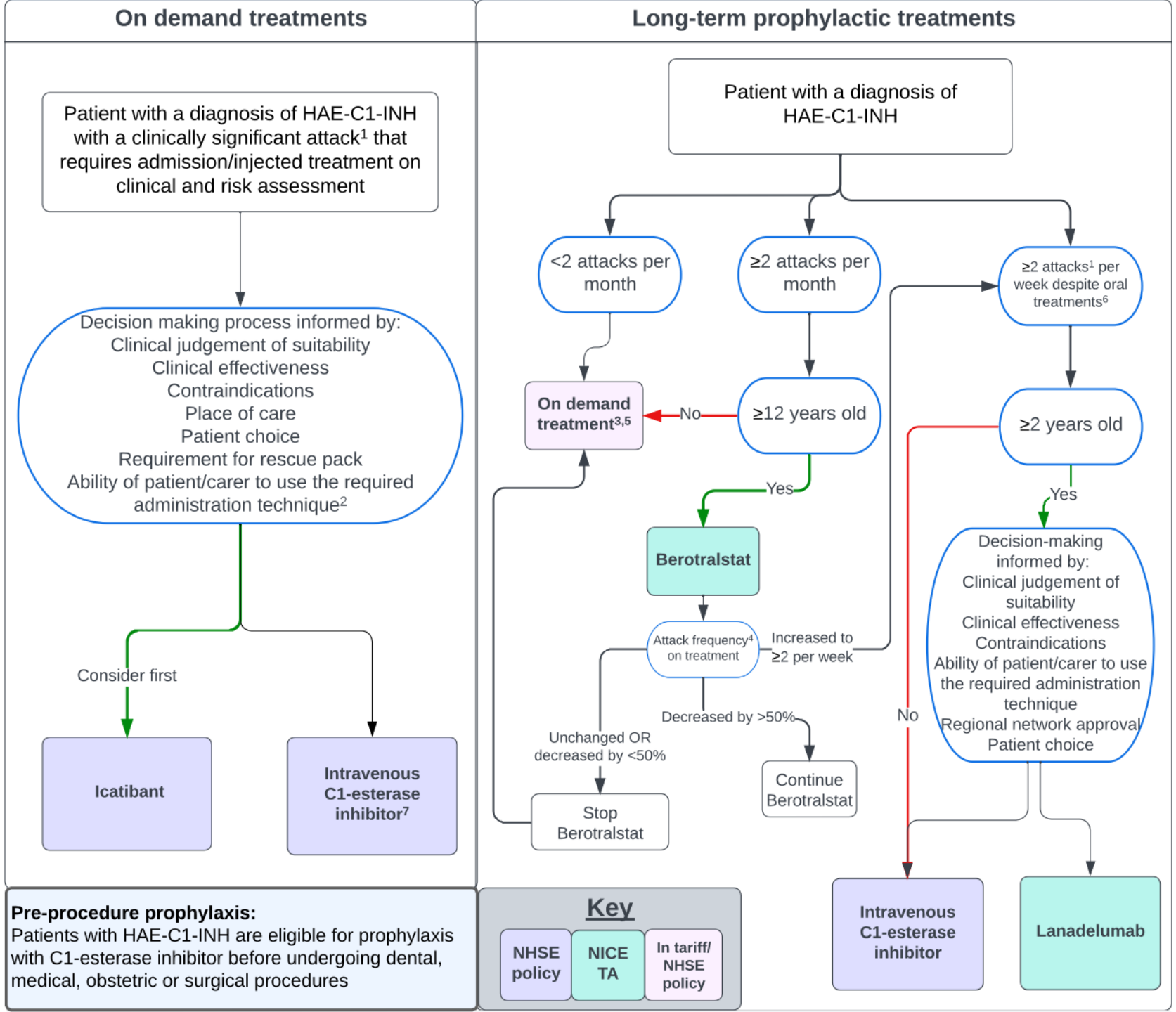
- Based on the estimated prevalence of 1:50,000 and a mid-year 2022 England and Wales population estimate of 60 million, a total of 1,041 people are estimated to be living with HAE in England and Wales
- Considering the proportion of people with HAE who are ≥12 years of age (86%), on LTP therapy ([redacted]), and experiencing ≥2 attacks per month at baseline (70%), an **estimated [redacted] people with HAE would be eligible for garadacimab in England and Wales in Year 1**

Abbreviations: HAE, hereditary angioedema; LTP, long-term prophylaxis

Back to main deck: Treatment pathway

NHSE algorithm of commissioned treatment options for HAE (February 2025)

- Framework to aid decision-making for angioedema specialists and patients
- Informed by regulatory status, NICE technology appraisal (TA) guidance and NHSE clinical commissioning policies
- All patients with a diagnosis of HAE-C1-INH should be under the care of specialised immunology centres as outlined in the service specification
- For special circumstances including pregnancy and lactation, please refer to individual product Summary of Product Characteristics
- Where plasma products used, patients need to consent to potential risks associated with these products
- Algorithm is not intended to guide management during critical events including airway- or life-threatening emergencies



HAE expert views and feedback – presented by company

Clinical experts agreed with company's proposed positioning of garadacimab

UK Delphi panel views on current treatment (Yong et al 2024):

- Views of 59 UK healthcare practitioners (30 consultants, 1 immunology nurse, 26 immunology clinical nurse specialists and 2 advanced nurse practitioners)
- Current access criteria for LTP options solely determined by attack frequency – too simplistic and disadvantages cohort of patients who would significantly benefit from LTP but are unable to access it
- Existing NICE recommendations and commissioning policies in UK mean that recommendations in international HAE guidelines (WAO/EAACI) cannot be fully recognised in all patients
- Prophylaxis policy in UK is far more stringent and restrictive compared to other countries – disadvantage

Feedback from 3 clinical experts in England on company's proposed positioning of garadacimab:

- HAE experts supported a broadly placed product, highlighting their desire for offering choices to patients and making management of their patients easier
- [redacted]

Abbreviations: EAACI, European Academy of Allergy and Clinical Immunology; HAE, hereditary angioedema; LTP, long-term prophylaxis; WAO, World Allergy Organization

Back to main deck: Clinical trial results

Clinical trial participants

Baseline characteristics of VAGUARD ITT population

Table: Demographic characteristics of trial participants

	Garadacimab (N=39)	Placebo (N=25)
Mean age, years (SD)	43.3 (17.5)	37.8 (12.8)
Age at diagnosis, % <18 years 18 to <40 years 40 to <65 years ≥65 years	[redacted]	[redacted]
Female, %	62	56
Mean weight*, kg (SD)	[redacted]	[redacted]
Bodyweight, % <50 kg 50 to <75 kg 75 to <100 kg ≥100 kg	[redacted]	[redacted]
Race, % White Other	85 15	88 12

Table: HAE history of trial participants

	Garadacimab (N=39)	Placebo (N=25)
HAE subtype, % Type I Type II	 87 13	 88 12
Prophylactic treatment ≤3 months before trial, %	36	28
Number of HAE attacks ≤3 months before trial, % Number observed Mean (95% CI)	 39 8.6 (6.3, 10.9)	 25 9.3 (6.4, 12.2)
Had laryngeal attacks, %	54	68
Location of HAE in ≤3 months before trial, % Cutaneous Abdominal Throat, larynx or tongue Peripheral	 77 77 33 8 3	 80 72 32 8 0

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; SD, standard deviation

Back to main deck: Clinical trial results

Post-hoc analysis of longer-term effects

Treatment effects continue beyond 6-month trial period

Figure: Percent reduction in time-normalised number of HAE attacks per month (VANGUARD/CSL312_3002 pooled population)

- Median (min, max) treatment duration of [redacted] months

Garadacimab (n=[redacted])

- Post-hoc analyses indicate efficacy of garadacimab in reducing time-normalised number of attacks from baseline is maintained beyond the randomised 6-month treatment period of VANGUARD with no evidence of waning of effect even after >2 years of treatment → mitigates uncertainty associated with relatively short treatment period of VANGUARD study

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Abbreviations: CI, confidence interval; n, number

Abbreviations: CI, confidence interval; HAE, hereditary angioedema; SD, standard deviation

Back to main deck: Key issues

Key issue 2: Methods and trials used in ITC

Company aligns with EAG after TE by removing phase 2 trial from ITC

Company – updated approach after TE to align with EAG

- Lack of head-to-head trials of garadacimab compared with LTP agents, so ITC used
- Original approach: preferred ITC was FE NMA which included phase 2 trial (CSL312_2001)
  - Also presented: ML-NMR using IPD and aggregate data to adjust for between study differences. EAG requested analysis without phase 2 trial but this was not provided
- After TE: aligned with EAG by removing phase 2 trial from ITC – now preferred in updated base case
  - See Appendix: Company FE NMA for attack rate and Company NMA results for all outcomes

EAG comments

- Preferred ITC is FE NMA with phase 2 trial removed based on model fit and heterogeneity between garadacimab trials. Had a minor impact on cost-effectiveness results
- Company's ML-NMR offered distinct methodological benefits in capturing and adjusting for heterogeneity and contextual factors compared with NMA. But EAG had concerns about pooling of garadacimab trials, testing of covariates, and inclusion of only a single covariate in final model for principal efficacy outcomes
  - ML-NMR used in a scenario (pre-TE) – did not impact overall cost-effectiveness results

Comparator company – BioCryst (berotralstat)

- Limitations and biases associated with ITC including heterogeneity between studies – uncertainty in results

Is the committee satisfied that this issue is resolved, now that company and EAG are aligned in using FE NMA excluding garadacimab phase 2 trial to inform their base case analyses?

Appendix: Methods and trials used in ITC,
Appendix: Company NMA results for all outcomes

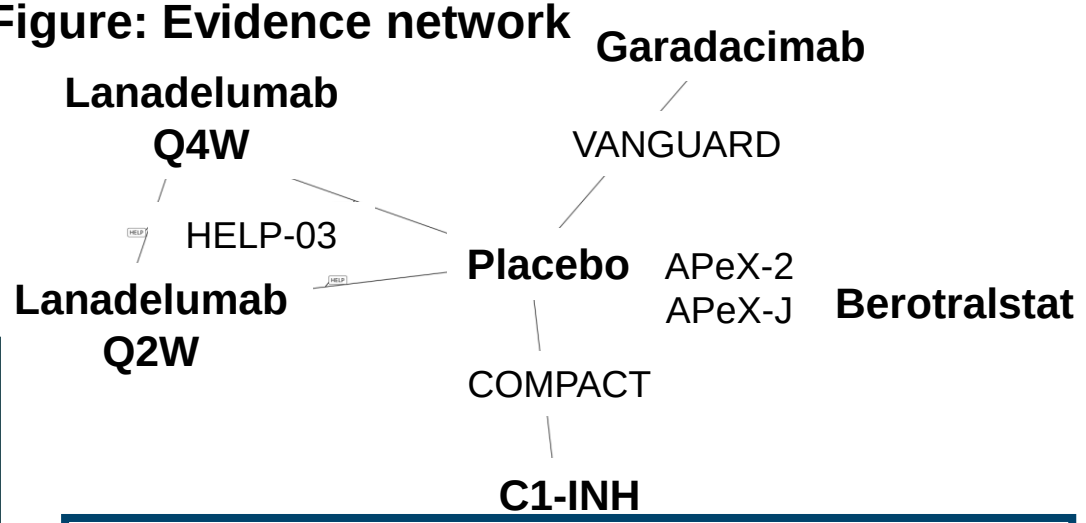
Company FE NMA for attack rate

Results of ITC with phase 2 trial excluded

- Time-normalised number of HAE attacks was used to calculate attack rate in company and EAG base case

Figure: Forest plot of time-normalised number of HAE attacks

Figure: Evidence network



Company

- Garadacimab and lanadelumab Q2W were [redacted]
- SC Berinert was [redacted] garadacimab or lanadelumab Q2W
- Lanadelumab Q4W [redacted], is not a first-line LTP and instead is used as reduced dose option for people in whom lanadelumab Q2W was effective
- Berotralstat was [redacted] than other active treatments

NHSE: Due to company's redactions for confidentiality [in TE documents] ITC results are unknown, so company's conclusions on comparative effectiveness cannot be confirmed or refuted

Abbreviations: C1-INH, C1-esterase inhibitor; CrI, credible interval; FE, fixed effects; NMA, network meta-analysis; Q2/4W, every 2 or 4 weeks; RR, relative risk; SC, subcutaneous

Appendix: Methods and trials used in ITC

Company NMA results for all outcomes

Overall results of NMAs (includes garadacimab phase 2 trial)

- FE NMA: [redacted]. Result of RE NMA similar but much wider credible intervals, as expected

[redacted]

Figure: Summary of pair-wise results from FE and RE NMAs – garadacimab vs comparators

[redacted]

Abbreviations: C1-INH, C1-esterase inhibitor; CrI, credible interval; FE, fixed effects; garad., garadacimab; NMA, network meta-analysis; Q2/4W, every 2 or 4 weeks; RE, random effects; RR, relative risk; SC, subcutaneous

Back to main deck: Key issues

Key Issue 3: Methods and data used to estimate treatment effectiveness

Company aligns with EAG after TE on methods and data used

Company – updated approach after TE to align with EAG

Base case	Cycle	Methods and data used
Company original submission	1 to 24	Constant attack rates for all treatments from time-normalised numbers of HAE attacks and NMA
	25+	Average attack rate reduction carried forward (AARRCF) for garadacimab, LOCF for comparators
Company updated after TE + EAG preferred	1 to 24	Observed attack rates from garadacimab OLE study, then apply FE NMA for time-normalised HAE attack rates to differentiate treatments and derive expected comparator outcomes
	25+	'Partial AARRCF' methodology based on garadacimab attack rates between cycles 12 and 24, then apply FE NMA for time-normalised HAE attack rates (as in cycle 1 to 24)

- Updated approach means all patients on berotralstat after month 3 have long-term attack free outcomes of lanadelumab Q2W for lifetime – not appropriate so uses alternative berotralstat modelling in Key issue 4

EAG comments – satisfied with company's updated approach

- Long-term effectiveness uncertain for all treatments. Garadacimab attack rates stable after first 6 months of treatment in OLE study (median [redacted] months treatment), but is a post-hoc analysis of small sample
- Company's original approach: did not fit data well as attack rates not constant in VANGUARD trial, they reduced over time. Different assumptions used for garadacimab and comparators from cycle 25 → bias

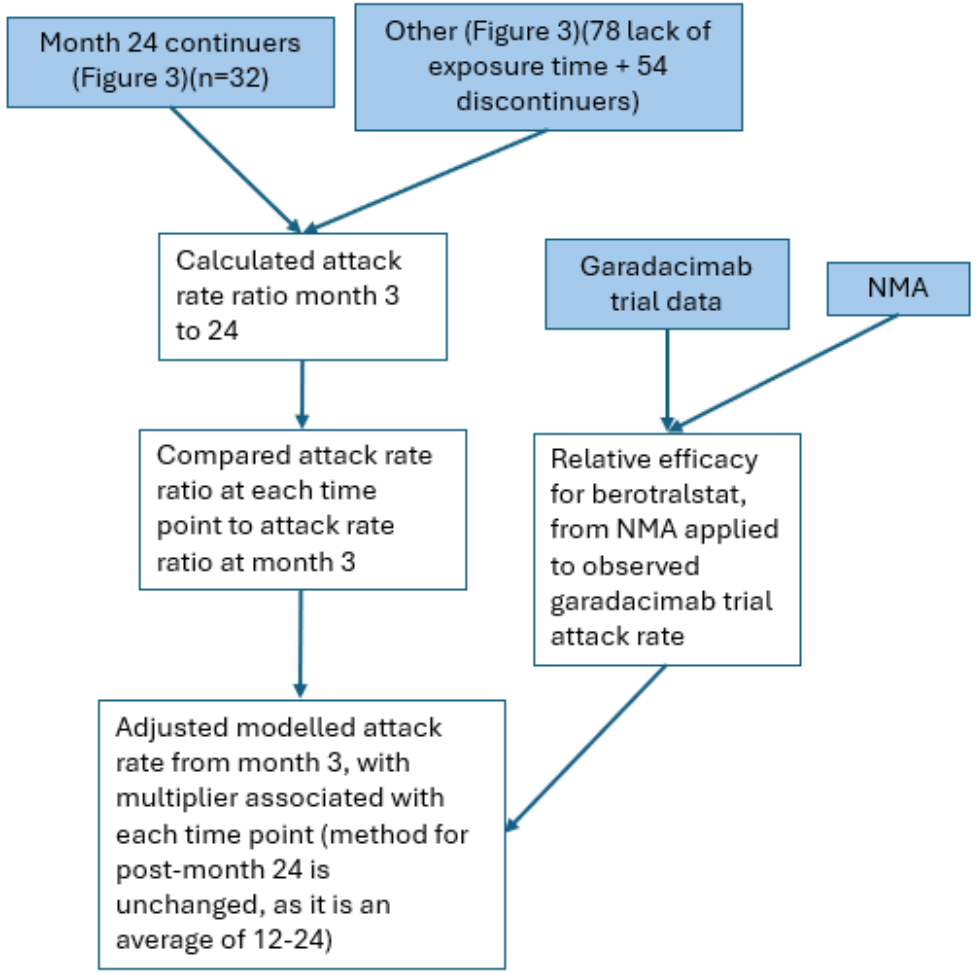
Is the committee satisfied that this issue is resolved, now that company and EAG are aligned in methods and data used to estimate treatment effectiveness?

Abbreviations: AARRCF, average attack rate reduction carried forward; FE, fixed effects; HAE, hereditary angioedema; LOCF, last observation carried forward; NMA, network meta-analysis; OLE, open-label extension; Q2W, every 2 weeks

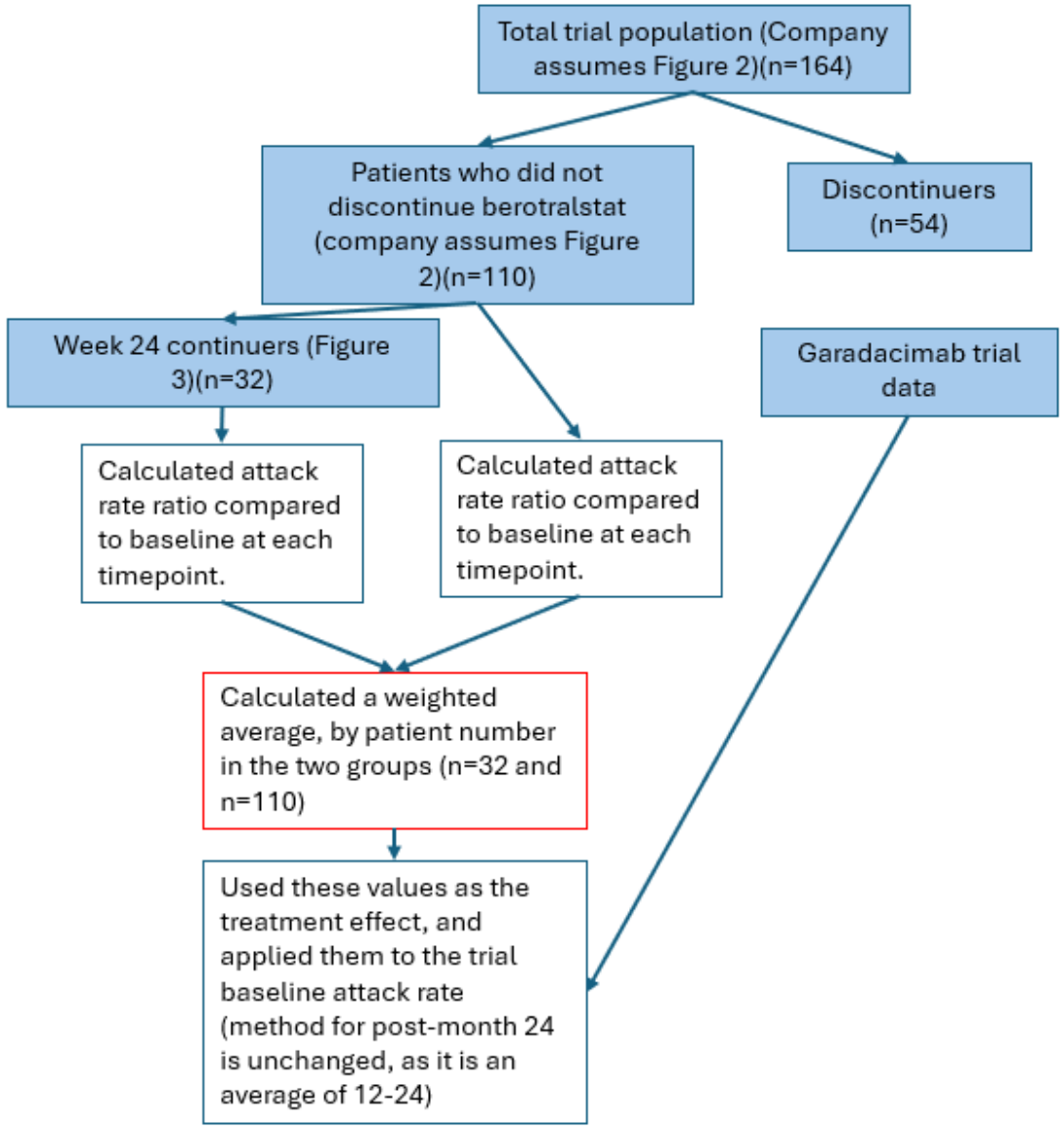
Back to: Key issue 4: Handling of berotralstat stopping rule

EAG's comparison of methods for using data from Elbashir poster to model berotralstat maintenance response

EAG approach



Company approach



Abbreviations: CI, confidence interval; n, number

Back to: Key issue 4: Handling of berotralstat stopping rule

Elbashir poster Figures 2 and 3

Figure 2. Average number of HAE attacks

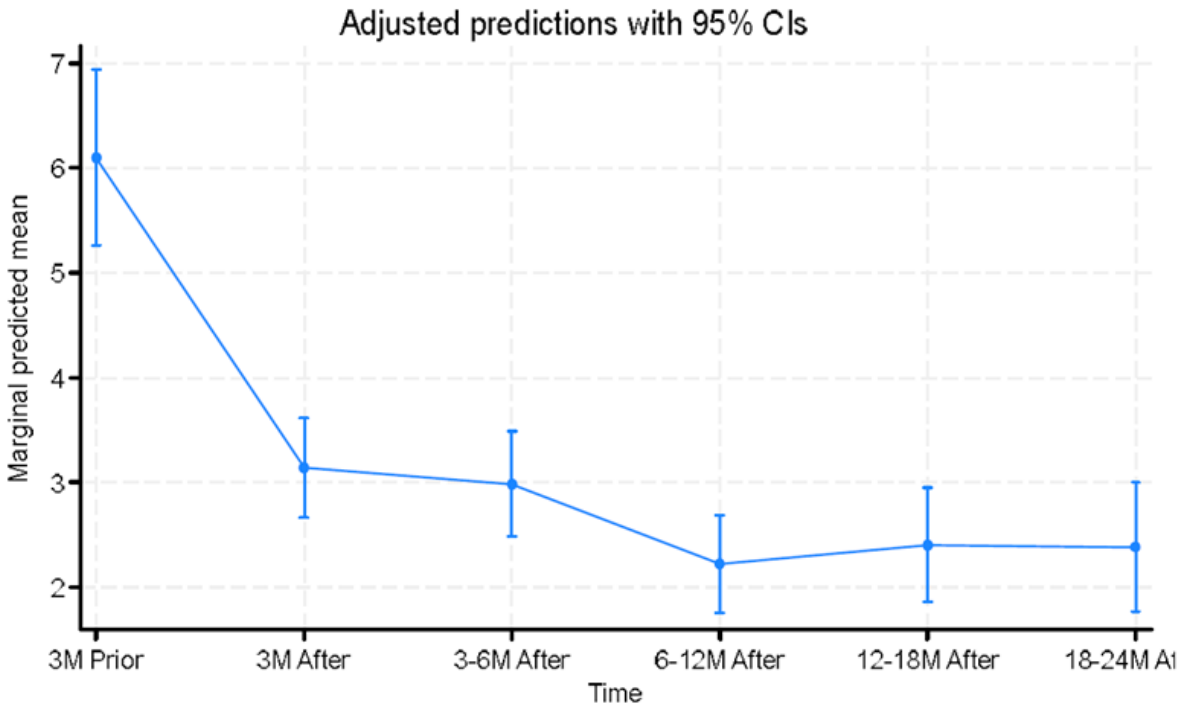
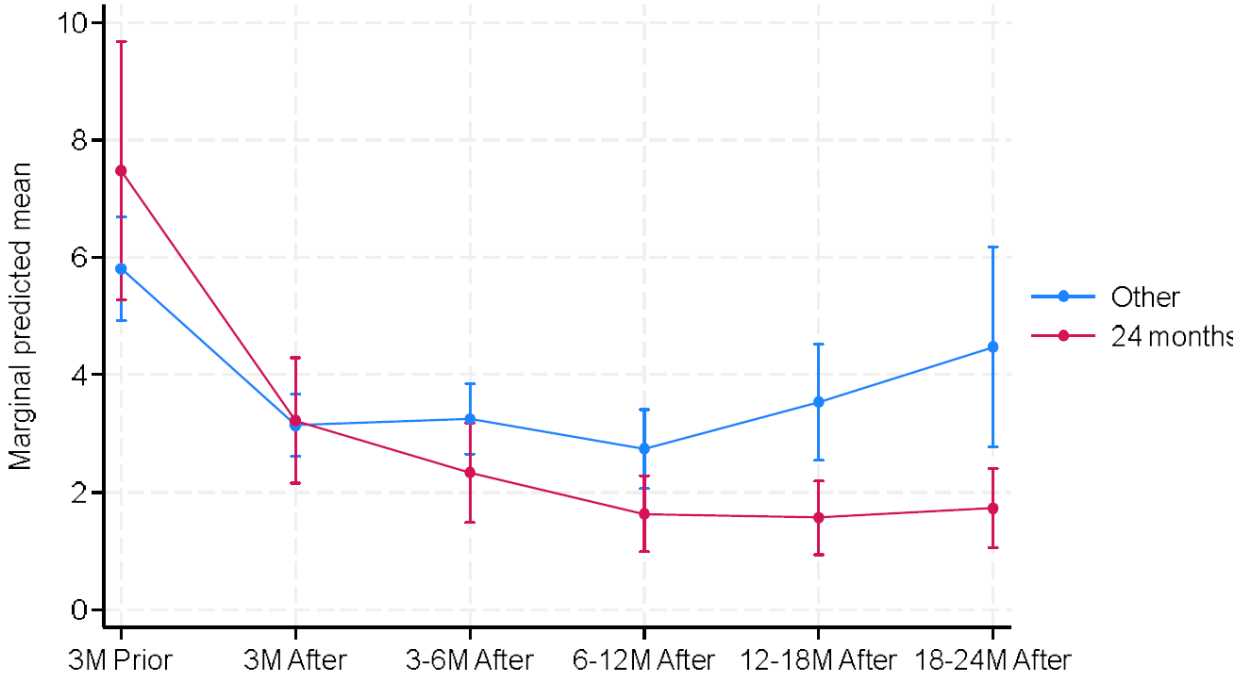


Figure 3. mixed Poisson regression chart for HAE attacks of the 32 patients vs total cohort



Abbreviations: CI, confidence interval; n, number

Key issue 6: Calculation of patient utilities

≥2 attacks per **month** | Large impact

Summary of differences in implementation of Nordenfelt utilities

Table: EAG's summary of approach implemented by company and EAG after TE

Feature	Company base case	EAG preferred approach
How HAE attack disutility calculated from Nordenfelt	Assumed that coefficient 'attacks in past cycle' meant attacks in **past month**	Assumed that coefficient 'attacks in past cycle' meant attacks in **past year**
Impact of attack rate on patient utility over time	**Time spent attack-free incorporated** • **Tunnel states*** added to model, in which patients gradually converge on general population utility over 6 months if they remain attack free	**Utility is a function of number of previous attacks** • Patients who are 6 months attack free have a higher utility than patients who are 1 month attack free
Calculation of general population utility	Estimated using standard formula from Ara and Brazier (2010)	Estimated using age coefficient from Nordenfelt, applied to intercept of 1
Maximum utility of patients in garadacimab arm	Patients in garadacimab arm who have not had an attack by month 12 achieve a utility value [redacted] lower than general population ([redacted] vs [redacted]), due to AEs	Patients in garadacimab arm who have not had an attack by Month 12 achieve a utility value [redacted] lower than general population ([redacted] vs [redacted]), due to AEs

*Tunnel states in the model house patients who have not had an attack in successive cycles

Note: Above it is stated that EAG assumed 'attacks in past cycle' meant 'attacks in past year' – this was cited in EAG report as being more logical. After ACM1 the EAG clarified that its base case assumed 'attacks in past month' (as company did), because when it tested both scenarios, 'attacks in past year' yielded negative utility values, which it did not consider credible.

Abbreviations: AEs, adverse events; HRQoL, health-related quality of life

Summary of company and EAG modelling of caregiver disutility

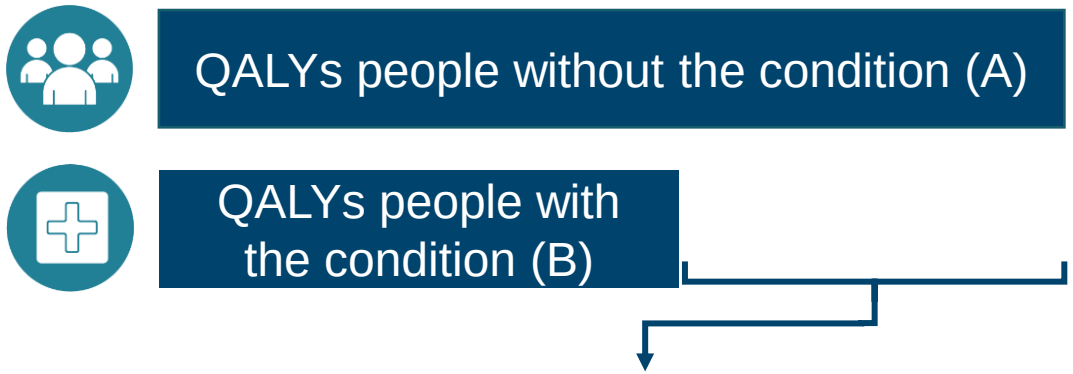
Table: Differences in assumptions between company and EAG base cases – unchanged after TE

Variable	Company base case	EAG base case
Key source for caregiver disutility	Lo et al 2022: Used vignettes specifically designed to describe the HAE context	Pennington et al 2024: Used SF-6D to measure utilities from UK Household Longitudinal Study
General population utility value for the median age carer	0.907	0.907
Unscaled caregiver disutility per HAE attack	0.145	0.0123 for every 0.1 patient disutility
Average number of carers per household	1.46	1
% of HAE attacks requiring caregiver assistance (aged 12–18 years old)	52.4%	52.4%
% of HAE attacks requiring caregiver assistance (ages ≥18 years old)	All severe non-laryngeal and laryngeal attacks	All severe non-laryngeal and laryngeal attacks

Back to: Company cost-effectiveness results

QALY weightings for severity

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Company and EAG agree:

- Criteria for severity weighting not met

Back to: Company cost-effectiveness results

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.