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

For public – contains ■ redacted information

Second appraisal committee C [12 August 2025]

Chair: Richard Nicholas

External assessment group: PenTAG

Technical team: Catherine Spanswick, Eleanor Donegan, Ross Dent

Company: CSL Behring

© NICE 2025. All rights reserved. Subject to Notice of rights.

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

- ✓ **Background and ACM1 recap**
- ❑ Consultation responses (excluding company)
- ❑ Company response and key issues
- ❑ Cost effectiveness results
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Draft guidance recommendations

Garadacimab **should not be used** to prevent recurrent attacks of hereditary angioedema in people 12 years and over

RECAP of committee considerations:

- There are 2 subpopulations by frequency of HAE attacks: garadacimab was cost effective in ≥2 attacks per week subpopulation but not in ≥2 attacks per month subpopulation
- Committee concluded garadacimab was not cost effective in whole population and was therefore not recommended
- Company's proposed positioning of garadacimab and its comparators, determined by attack frequency, was appropriate
- EAG's exploration of 2nd-line garadacimab after berotralstat, compared with no preventive treatment, reasonable to consider

Abbreviations: HAE, hereditary angioedema

Committee preferred assumptions at ACM1 with company approach at ACM2

- Company's overall model structure with 3 primary health states was acceptable for decision making

Committee preferred assumptions at ACM1	Adopted by company at ACM2?
Berotralstat long-term effectiveness and stopping using EAG's scenario based on the Elbashir et al. poster	No, but updated approach uses new IPD for relevant cohort from Elbashir → **key change to ACM2 base case**
EAG's approach for instant lanadelumab dose switching from Q2W to Q4W at 12 months and equivalent efficacy	No, company approach unchanged, differs from EAG on timing & efficacy
Patient utilities • For an attack: asked company and EAG to provide more information on attack disutility values they assumed • Attack free utility: EAG's approach (without tunnel states)	No, company approach unchanged
EAG's carer disutility approach (1 carer, Pennington et al. [2024])*	No, company approach unchanged (but company also assumed 1 carer)

*Correction from ACM1: company adopted 1 carer per household at TE, so is aligned with committee on this

Abbreviations: ACM1/2, 1st/2nd committee meeting; IPD, individual patient data; TE, technical engagement; Q2/4W, every 2 or 4 weeks

Key issues for committee discussion at 2nd committee meeting

Section	Issue (EAG report issue number)	ICER impact within EAG model	
		≥2 attacks per **month**	≥2 attacks per **week**
Decision problem	Uncertainty around sequencing in treatment pathway for people with HAE (1)	Large	N/A
Cost effectiveness	Handling of berotralstat stopping rule (4)	Large	N/A
	Lanadelumab switching between Q2W and Q4W (5)	N/A	Small
	Calculation of patient utilities (6)	Large	Small
	Calculation of caregiver disutility (other)	Small	Small
	Baseline HAE attack rate in model (other)	Large	N/A

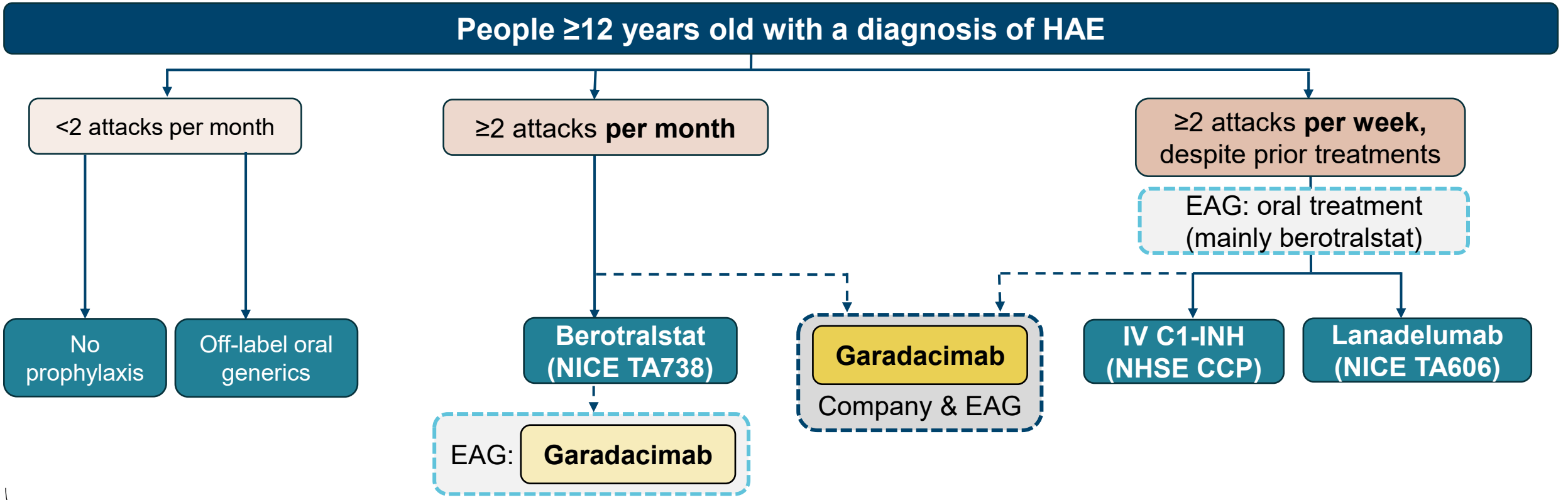
Uncertainties and additional sources of evidence identified by the company include:

- Individual patient-level data (IPD) from Elbashir et al. (2024) to inform berotralstat efficacy assumptions
- Clinical consensus statement signed by 8 UK clinical HAE experts in the UK, includes comments on clinical benefit of garadacimab and differentiation from existing options, treatment sequencing preferences
- Consideration of impact of baseline attack rate in cost-effectiveness analysis

NICE

Abbreviations: HAE, hereditary angioedema; ICER, incremental cost-effectiveness ratio; N/A, not applicable; Q2W / Q4W, every 2 / 4 weeks

Treatment pathway for long-term prophylaxis of HAE



Appendix: NHSE commissioning algorithm

Abbreviations: C1-INH, C1-esterase inhibitor; CCP, clinical commissioning policy; HAE, hereditary angioedema; IV, intravenous; LTP, long-term prophylaxis; NHSE, NHS England

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

- ❑ Background and ACM1 recap
- ✓ **Consultation responses (excluding company)**
- ❑ Company response and key issues
- ❑ Cost effectiveness results
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Summary of consultation responses

From: British Society for Immunology Clinical Immunology Professional Network; Hereditary Angioedema UK; NHS England Immunology and Allergy Clinical Reference Group; Royal College of Pathologists; Takeda UK

Theme	Comments
Every person with HAE is different	• Berotralstat (≥2 attacks per month) and lanadelumab (≥2 attacks per week) do not suit all people with HAE. Need for additional treatment options
Unmet need	• Significant for people having <2 attacks per week; 1/3 of people stop berotralstat due to lack of efficacy or unacceptable side effects (Elbashir) • NICE guidance and commissioning based on attack frequency, not severity. People not reaching commissioned frequency left with invasive IV C1-INH • Easy to administer treatment, particularly adolescents and younger adults: key times of life for education & for managing breakthrough attacks due to fluctuating oestrogen
Value of LTP treatments	• LTPs provide expectation and realisation of reduced HAE attacks, but not a cure • Consider Walsh et al. 2025 ITC results for garadacimab vs comparators → see next slide
Key issues	• Comments on key issues 1, 4, 5 and 6 summarised on corresponding slides • Attacks can last 1 to 4 days with prolonged severe fatigue / flu-like symptoms → severe impact on QoL
Cost-effectiveness	• Would like to see result of comparing garadacimab with no LTP (≥2 attacks per month) • Cost-benefit of lanadelumab likely overestimated • Proposed uncaptured aspects summarised on later slide

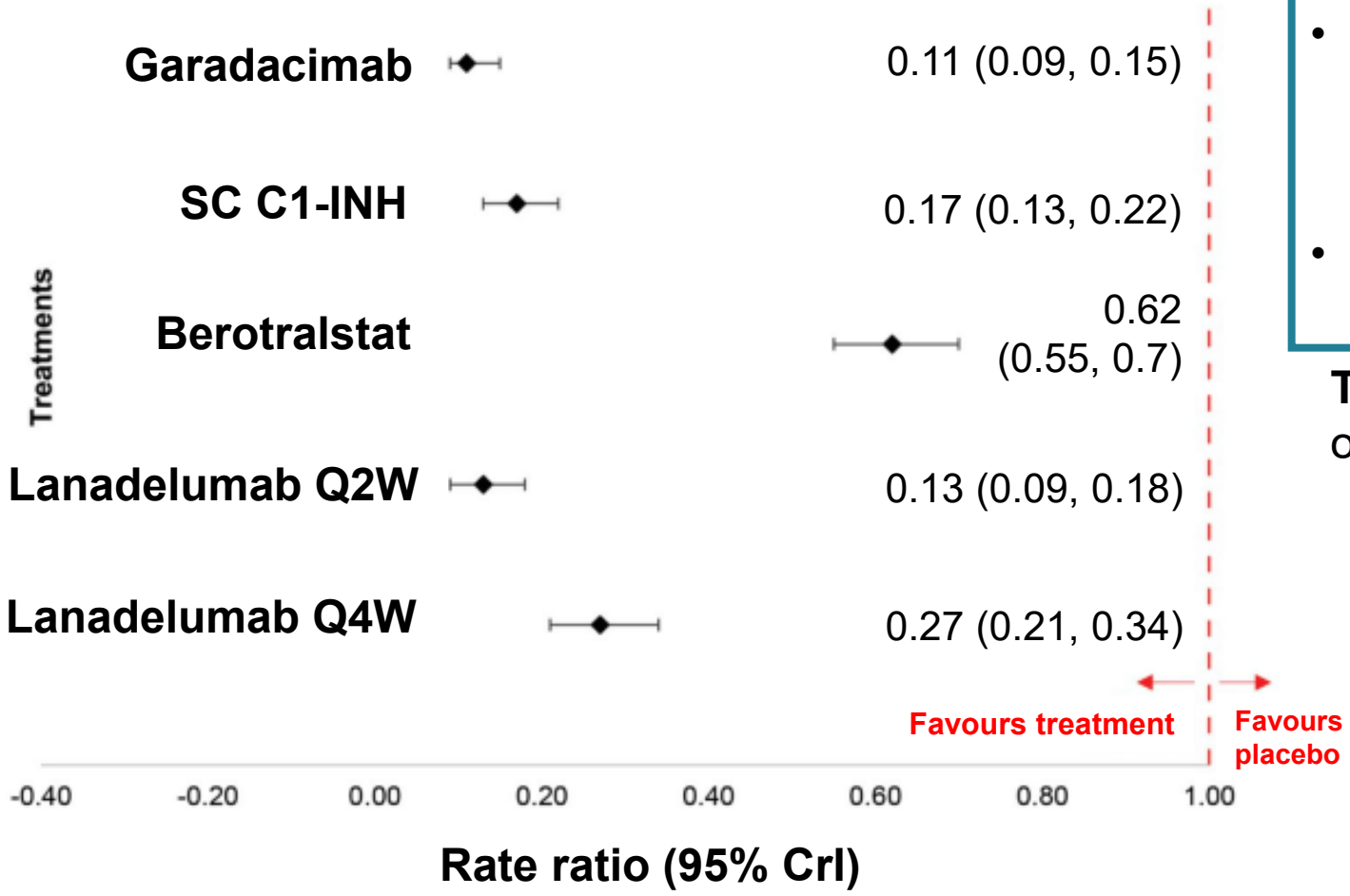
Abbreviations: C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; ITC, indirect treatment comparison; IV, intravenous; LTP, long-term prophylaxis; Q2W, every 2 weeks

Company published NMA (Walsh et al 2025)

Not ITC used in model

Results of ITC with phase 2 trial included

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



Background:

- NMA results presented on this slide include a phase 2 trial that was excluded by EAG (and company) in ITC used in modelling
- Confidentiality marking in company's submissions prevented a summary of results of FE NMA used in model from being presented publicly including in draft guidance
- See Appendix for ITC results used in model: NMA for attack rate and NMA for all outcomes

Table: Rank and rate ratio (95% CrI; significance) of time-normalised number of HAE attacks:

1. Garadacimab	0.88 (0.58 to 1.32; NS)
2. Lanadelumab Q2W	0.77 (0.50 to 1.16; NS)
3. SC C1-INH	0.64 (0.44 to 0.90; sig.)
4. Lanadelumab Q4W	0.43 (0.34 to 0.56; sig.)
5. Berotralstat	0.62 (0.55 to 0.70; sig.)
6. Placebo	

Abbreviations: C1-INH, C1-esterase inhibitor; CrI, credible interval; DG, draft guidance; FE, fixed effects; NMA, network meta-analysis; NS, not statistically significant; Q2/4W, every 2 or 4 weeks; SC, subcutaneous; sig. statistically significant

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

- ❑ Background and ACM1 recap
- ❑ Consultation responses (excluding company)
- ✓ **Company response and key issues**
  - New IPD on berotralstat responders
  - Commentary on committee preferred assumptions
  - No change to the confidential discount
- ❑ Cost effectiveness results
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Key issue 1: Uncertainty around sequencing in treatment pathway for HAE

≥2 attacks per month population: company maintains no modelling of sequencing

Committee at ACM1 (DG section 3.3)

- Company's proposed positioning of garadacimab and its comparators was appropriate
- EAG's exploration of 2nd-line garadacimab after berotralstat, compared with no LTP, reasonable to consider

Stakeholder comments from BSI-CIPN, NHS England IACRG & Hereditary Angioedema UK

- Would like to see cost-effectiveness results of comparing garadacimab with no LTP at 2nd line
- Wider clinical community not convinced by clinical expert statement in DG that majority of physicians would recommend berotralstat over garadacimab if both were available as 1st line options, given available data on efficacy and tolerability → prefer to offer garadacimab first. Shared decision making indicated by guidelines

Company – approach unchanged

- ≥2 HAE attacks per month: garadacimab and berotralstat are alternative options, without sequencing
- Sequencing is out of scope, both in methods and comparators, and not explored in other HAE appraisals
- Clinical experts at ACM1 suggested they might try berotralstat first, but should be patient-centric approach

EAG comments – approach unchanged

- Presents scenario: garadacimab 2nd-line after berotralstat, where 2nd-line garadacimab is compared with no LTP. Consistent with NHSE commissioning which prioritises oral treatment, including before lanadelumab

Should consideration of sequencing of garadacimab and berotralstat be incorporated in committee-decision making for people having ≥2 HAE attacks per month?

NICE

Abbreviations: ACM1, 1st appraisal committee meeting; BSI-CIPN, British Society for Immunology Clinical Immunology Professional Network; DG, draft guidance; HAE, hereditary angioedema; LTP, long-term prophylaxis; IACRG, Immunology and Allergy Clinical Reference Group; NHSE, NHS England

Key issue 4: Handling of berotralstat stopping rule (1/2)

Company updated approach uses individual patient data but EAG disagrees

Committee at ACM1 (DG section 3.10)

- TA738: berotralstat should be stopped if attack frequency not reduced by ≥50% after 3 months
- Agreement that model should reflect the impact of the stopping rule on the cost-effectiveness of berotralstat
- Preferred EAG's scenario using Elbashir et al. (2024) poster of UK real-world data, but highly uncertain

Stakeholder comments from BSI-CIPN

- Disagrees with EAG base case assumption that after month 3, berotralstat efficacy = lanadelumab Q2W

Company – approach updated using new data from Elbashir study

- Analysed anonymised IPD for berotralstat in people having ≥2 attacks per month at baseline

Note: The committee thanks company and experts for work done in obtaining this IPD data for consideration

EAG – approach updated using NMA

Time	Company updated base case	EAG updated base case
Up to month 3	NMA data for berotralstat efficacy, anchored to baseline	NMA data for berotralstat efficacy, anchored to garadacimab
From month 3	Elbashir IPD for Cohort 2: ≥50% reduction in attack rate at month 3 → relevant, responding cohort (IPD Appendix)	EAG believes truth lies between ITT analysis from NMA for berotralstat efficacy, and original EAG base case of assuming berotralstat = lanadelumab after month 3

Abbreviations: BSI-CIPN, British Society for Immunology Clinical Immunology Professional Network; DG, draft guidance; HAE, hereditary angioedema; IPD, individual patient data; ITT, intention to treat; LTP, long-term prophylaxis; NMA, network meta analysis; Q2W, every 2 weeks

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

Company updated approach uses individual patient data but EAG disagrees

EAG comments continued

From month 3:

- **Company** analysis using IPD gave results slightly worse for berotralstat than ITT analysis using NMA data without adjusting for stopping rule
- **EAG** consider company analysis lacks face validity. Elbashir data primarily influenced by negative effects of differences in trial design and patient population (naïve comparison), not positive influence of stopping rule
- **EAG** updated approach uses ITT analysis from NMA to represent realistic lower bound. EAG believes truth lies between this and original approach assuming berotralstat = Q2W lanadelumab (upper bounds)

Table: Impact of modelling berotralstat attack rate from month 3

Alternative approaches	Berotralstat total QALYs
Company analysis of Elbashir IPD	[redacted]
ITT NMA analysis for berotralstat (EAG lower bound)	[redacted]
Berotralstat = lanadelumab (EAG upper bound)	[redacted]

0-3 months: anchoring of NMA data (modest ICER impact)

- Company's updated approach anchors NMA berotralstat efficacy to baseline attack rate in trials. This will give biased results unless same method implemented for garadacimab

- Baseline attack rate in Elbashir real-world study higher than in trials – see Other issue

Which updated approach does committee prefer for modelling berotralstat effectiveness, up to month 3 and from month 3 onwards when stopping rule would apply in clinical practice?

NICE

Abbreviations: HAE, hereditary angioedema; IPD, individual patient data; ITT, intention to treat; NMA, network meta analysis; Q2W, every 2 weeks

Key issue 5: Lanadelumab switching between Q2W and Q4W

Differences in way company and EAG model switching have small ICER impact

Committee at ACM1 (DG section 3.11)

- Company's approach likely underestimated lanadelumab efficacy. Preferred EAG's assumptions

Stakeholder comments from BSI-CIPN

- EAG assumes lanadelumab switching to Q4W dosing occurs instantaneously at 12 months based on real world study in Germany. But in UK clinical practice, transition from Q2W to Q4W is gradual, if attacks stable
- Patients in Germany have lower baseline attack rates than UK (INTEGRATED study by Magerl et al. 2025)
- EAG assumes equal efficacy of lanadelumab Q4W and Q2W. Typically <50% in UK able to extend dosing to interval to Q4W and efficacy will drop in some of these patients even though previously stable on Q2W

Company – approach unchanged (Appendix)

- Disagrees with EAG about timing of dose switching, company assumes gradual not instantaneous, and about efficacy difference between Q2W and Q4W dosing, uses data for starting on Q4W not for switching

EAG comments – approach unchanged

- Tested timing of switching (gradual or instantaneous) in sensitivity analysis – has minimal ICER impact
- Q4W dosing = Q2W efficacy, with expectation that if people switching to Q4W dosing do not maintain response, they move back up to Q2W dosing. Data not available to support more sophisticated modelling

Does the committee maintain its preference for EAG's assumptions about lanadelumab dose switching?

NICE

Abbreviations: BSI-CIPN, British Society for Immunology Clinical Immunology Professional Network; DG, draft guidance; ICER, incremental cost effectiveness ratio; Q2/4W, every 2 or 4 weeks

≥2 attacks per **month**

Large impact (Nordenfelt coefficient)

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

Some differences in way company and EAG model patient utilities

Committee at ACM1 (DG sections 3.12 and 3.13)

- Potential double counting of HRQoL impact of treatment on attacks and on freedom from attacks
- For having an attack: Impact of attack should last 3.13 days (= company)
- For being attack free: EAG's approach (without using tunnel states) should be used in decision making

Company – approach unchanged (ACM1: Appendix)

- Considers no HRQoL overlap between calculating burden of having an attack and impact of attack freedom
- 8 UK clinical experts: reasonable that patient's QoL gradually improves over time they are attack-free

Nordenfelt coefficient – assumes past attacks were in 'past year':

- Noted that EAG clarified **after ACM1** that EAG assumed 'attacks in **past month**' not '**past year**'
- Nordenfelt paper describes 'annual attack frequency', which supports company contention that 'attacks per cycle' is the '**past year**'. Disagrees with EAG about relevance of negative utility scenarios when using '**past year**' where impact of attack is updated to 3.13 days

Tunnel states:

- Company maintains use of tunnel states to model freedom from attacks

EAG comments – approach unchanged

- Company attempted to **account for attack freedom in 2 ways** (Nordenfelt regression and tunnel states)

Abbreviations: ACM1, 1st committee meeting; DG, draft guidance; HRQoL, health-related quality of life

≥2 attacks per **month**

Large impact (Nordenfelt coefficient)

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

Some differences in way company and EAG model patient utilities

EAG comments continued

Nordenfelt coefficient – EAG assumes past attacks were in 'past month':

- Recognised ambiguity in interpretation from the source publication. So, EAG compared modelled health state utilities (table in Appendix)
  - Attacks in **past year** (company preferred) gave negative utility values for untreated 50-year old having ≥2 attacks per week in company's updated model → implausible
  - This may partly be a result of double counting

Use of tunnel states:

- Approach is inappropriate in EAG's view and instead EAG maintains approach without tunnel states where utility is a function of number of previous attacks (ACM1: Appendix)

Which approach does the committee prefer for accounting for freedom from attacks? Does the committee maintain its preference for this to be done without using tunnel states in the model (EAG). What it the committee's preferred interpretation of the Nordenfelt coefficient – attacks in past cycle are in past year (company) or past month (EAG)?

Abbreviations: HRQoL, health-related quality of life; QoL, quality of life

Other issue: Calculation of carer disutility

Differences in way company and EAG model carer utilities have small impact

Committee at ACM1 (DG section 3.14)

- Reasonable for carer disutility to be included. Preferred EAG's source, and 1 carer per household

Company – approach unchanged (ACM1: Appendix)

- Disutility source was Lo et al. (2022): vignettes specifically designed to describe the HAE context
- EAG suggested unscaled value (0.145) was large, but is adjusted for duration of HAE attacks requiring carer help, resulting in effective value approximately 9-fold smaller and in line with other HAE appraisals
- Use of HAE-specific evidence supported by company's statement from 8 UK clinical experts:
  - Care often provided by family members who also have HAE. Management of HAE and receiving care are connected and can influence patient and carer attacks. Most appropriate to consult sources of QoL evidence which have directly elicited quality of life when living with or caring for those with HAE

EAG comments – approach unchanged

- Prefers Pennington et al. (2024), which uses SF-6D to measure utilities in survey of UK households
- Disagrees with company's summary that suitable evidence is available from previous HAE appraisals
- Reiterates that whether to include carer utility values and their size has very limited impact on cost-effectiveness and was explored extensively in sensitivity analysis

Does the committee maintain its preference for EAG's source for carer disutility?

Abbreviations: ACM1, 1st committee meeting; DG, draft guidance; HAE, hereditary angioedema; QoL, quality of life; HAE, hereditary angioedema; SF-6D, short form 6 dimensions

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

Other issue: Baseline HAE attack rate in model

EAG uses updated approach based on Elbashir IPD

Slide updated vs circulated version

Background (DG section 3.18)

- Not discussed at ACM1 and not reported as a key issue in original EAG report

Company – approach updated after EAG critique circulated

- **ACM1 and DG response:** assumed baseline HAE attack rate [redacted] per month, based on VANGUARD trial
- Notes high baseline attack rate ([redacted]) in Elbashir IPD cohort 2 (key issue 4), vs that observed in trials
- Suggested scenario to align with TA738 (3.1 per month, berotralstat APeX trial) to reduce uncertainty
- **After receiving EAG critique (below):** requested to incorporate EAG value into updated base case

EAG comments – assumption updated

- Explained that a higher baseline attack rate in model is more favourable to garadacimab
- EAG's updated assumption uses baseline attack rate from Elbashir (ITT IPD) = [redacted] per month, which it considered best source of evidence being a UK real-world study, so more likely to be representative of UK clinical practice than a trial
- Analysis used ≥2 attacks per month at baseline population of IPD, in people who began treatment after positive reimbursement decision → improved QALY benefit for garadacimab versus berotralstat

Which baseline HAE attack rate should be implemented in the modelling?

NICE

Abbreviations: DG, draft guidance; HAE, hereditary angioedema; IPD, individual patient data; ITT, intention to treat; QALY, quality-adjusted life year

ACM2 summary of updated company and EAG base cases

Table: Differences in assumptions between company and EAG base cases – updated for ACM2

Assumption	Company updated base case	EAG updated base case
Positioning of garadacimab	Does not consider sequencing for garadacimab vs berotralstat	Scenario explores 2nd-line garadacimab after berotralstat, versus no LTP
Model structure	3 primary health states; 'alive without an attack' state included 6 tunnel states	3 primary health states without tunnel states
Baseline attack frequency	**New at ACM2** (differs from DG response): [redacted] per month = EAG	**New at ACM2:** [redacted] per month (real world evidence, Elbashir, ITT IPD)
Handling of berotralstat data and stopping rule	**New at ACM2:** Up to month 3, NMA data anchored to baseline **New at ACM2:** From month 3, IPD data from Elbashir study (Cohort 2)	Up to month 3, NMA data anchored to garadacimab **New at ACM2:** From month 3, NMA data using ITT analysis
Lanadelumab dose switch, Q2W and Q4W	Gradual switch over 12 months. Efficacy = people starting on Q4W in HELP trial	Instantaneous switch at 12 months. Efficacy, Q4W = Q2W dosing in model
Patient utility values	Past cycle = past year. Incorporates attack freedom using 6 tunnel states	Past cycle = past month. Incorporates attack freedom without tunnel states
Caregiver disutility, per qualifying HAE attack	Lo et al 2022: unscaled disutility of 0.145, adjusted for attack duration	Pennington et al 2024: disutility of 0.0123 for every 0.1 patient disutility

NICE

Abbreviations: ACM2, 2nd committee meeting; HAE, hereditary angioedema; IPD, individual patient data; ITT, intention to treat; LTP, long term prophylaxis; NMA, network meta analysis; Q2/4W, every 2 or 4 weeks

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

- ❑ Background and ACM1 recap
- ❑ Consultation responses (excluding company)
- ❑ Company response and key issues
- ✓ **Cost effectiveness results**
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Summary of cost-effectiveness results at ACM2

Slide updated vs circulated version

Garadacimab not cost-effective for ≥2 attacks per month population in updated EAG base case, but cost-effective for ≥2 attacks per week population

Recap of ACM1: Acceptable ICER is around **middle of the range** £20,000 to £30,000 per QALY gained

- No change to the confidential discount at ACM2

≥2 HAE attacks <u>per month</u> population (including garadacimab PAS and cPAS):

- Updated: EAG has explored impact of late change to baseline attack frequency on company base case, which makes it more cost effective. **Committee will consider all confidential ICERs in Part 2**
- EAG base case ICER for garadacimab versus berotralstat substantially higher than £30,000/QALY
    - EAG scenario: 2nd-line garadacimab not cost-effective versus no LTP (after 1st-line berotralstat)

≥2 HAE attacks <u>per week</u> population (including garadacimab PAS and cPAS):

- Garadacimab dominated in company and EAG base cases (vs comparators)

As at ACM1: QALY weighting for severity does not apply and company has not made a managed access proposal for garadacimab

NICE

Abbreviations: ACM1/2, 1st/2nd committee meeting; C1-INH, C1-esterase inhibitor; c/PAS, confidential/ patient access scheme; DG, draft guidance; HAE, hereditary angioedema; ICER, incremental cost-effectiveness ratio; LTP, long term prophylaxis; QALY, quality-adjusted life years

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

- ❑ Background and ACM1 recap
- ❑ Consultation responses (excluding company)
- ❑ Company response and key issues
- ❑ Cost effectiveness results
- ✓ **Other considerations**
- ❑ Summary

NICE National Institute for Health and Care Excellence

Back to : Summary of consultation responses

Proposed uncaptured aspects at ACM2

Noted by stakeholders and in company's statement from 8 UK clinical experts

Proposed uncaptured aspects	Related considerations
Convenience • Garadacimab autoinjector may be stored at room temperature for a single period of up to 2 months • Convenience (combined with efficacy) offers step change in management of HAE particularly subpopulation having ≥2 attacks per month	• Could lift key restrictions on patients in terms of travelling to work, school, visiting family and for leisure purposes • Convenience is in relation to lanadelumab. Berotralstat is an oral treatment
Unmet need in specific age groups • People aged 12 to 16 years appear to have more side effects with berotralstat than older patients • People aged 12 to 25 years, in particular those with attacks triggered by fluctuation of oestrogen, can more easily manage attacks with SC LTP at home	• Equality considerations – see recap of ACM1
HRQoL • Outcomes related to attack severity • Anticipatory anxiety and PTSD effects associated with potential HAE attacks	• Company incorporated treatment differences for attack severity

Abbreviations: ACM2, 2nd appraisal committee meeting; HAE, hereditary angioedema; PTSD, post-traumatic stress disorder

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

- ❑ Background and ACM1 recap
- ❑ Consultation responses (excluding company)
- ❑ Company response and key issues
- ❑ Cost effectiveness results
- ❑ Other considerations
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Key issues for committee discussion at 2nd committee meeting

Section	Issue (EAG report issue number)	Status	ICER impact within EAG model	
			≥2 attacks per **month**	≥2 attacks per **week**
Decision problem	Uncertainty around sequencing in treatment pathway for people with HAE (1)	For committee discussion	Large	N/A
Cost effectiveness	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
	Calculation of carer utilities (other)	For committee discussion	Small	Small
	Baseline HAE attack rate in model (other)	For committee discussion	Large	N/A

Abbreviations: HAE, hereditary angioedema; ICER, incremental cost-effectiveness ratio; Q2W / Q4W, every 2 / 4 weeks

Key questions for committee at ACM2

Section	Key questions
Decision problem	Should consideration of sequencing of garadacimab and berotralstat be incorporated in committee-decision making for people having ≥2 HAE attacks per month?
Cost effectiveness evidence	Which updated approach does committee prefer for modelling berotralstat effectiveness, up to month 3 (anchored to garadacimab [EAG] or baseline [company]) and from month 3 onwards (ITT NMA [EAG] or Elbashir IPD [company]) when stopping rule would apply in clinical practice?
	Does the committee maintain its preference for EAG's assumptions about lanadelumab dose switching? Impact is small. EAG assumes instantaneous switching at 12 month, and efficacy with Q4W = Q2W dosing.
	Which approach does the committee prefer for patient utilities, noting that key difference relates to interpretation of Nordenfelt coefficient and use of tunnel states?
	Does the committee maintain its preference for EAG's source for carer disutility?
	Which baseline HAE attack rate should be implemented in the modelling? Company prefers to align with EAG, EAG uses real world data.
Cost effectiveness results	Will the committee consider making a recommendation in a subpopulation (i.e. people having ≥2 attacks per week) if it cannot make a recommendation in the overall population (i.e. including people having ≥2 attacks per month)

Abbreviations: HAE, hereditary angioedema; NMA, network meta analysis; Q2W / Q4W, every 2 / 4 weeks

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

Supplementary appendix

S1. Appendices for ACM2
S2. Recap of ACM1

NICE National Institute for Health and Care Excellence

Back to main deck: Company published NMA

RECAP

Company FE NMA for attack rate

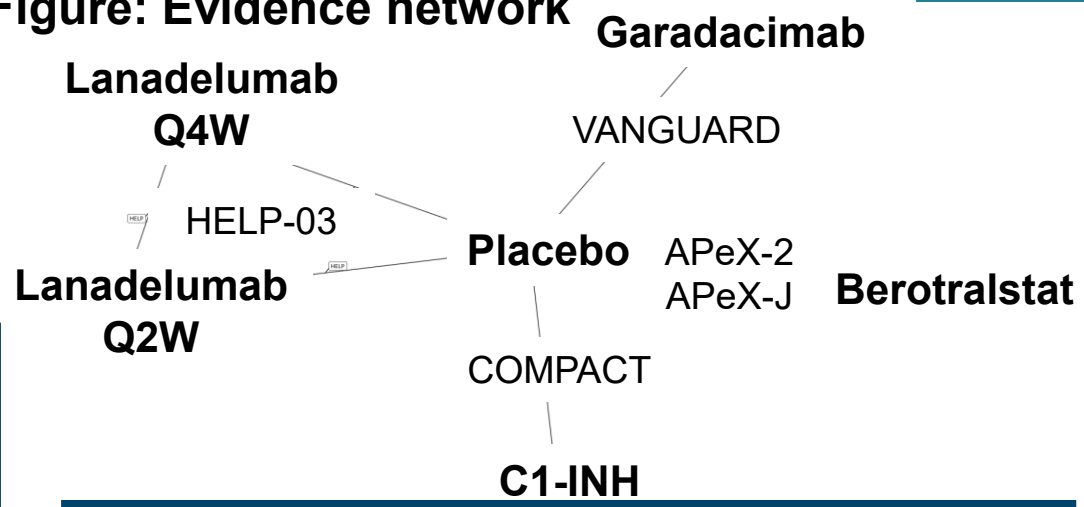
Results of ITC with phase 2 trial excluded

- 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

[redacted]

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

Company NMA results for all outcomes

RECAP

[redacted]

Overall results of NMAs (includes garadacimab phase 2 trial)

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

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 issue 4

IPD analysis of real-world berotralstat use (Elbashir)

Results for Cohort 2: people having ≥50% reduction in HAE attack rate at month 3

Table: HAE attack rate reduction from baseline

Cohort 2	Time after starting berotralstat				
	3 months	3–6 months	6–12 months	12–18 months	18–24 months
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean reduction, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinuation due to:					
Efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety					
Efficacy and safety					
Other					

[redacted] patient(s) discontinuing in month 24 or beyond due to [redacted]

Company comments

- [redacted]

Abbreviations: HAE, hereditary angioedema; IPD, individual patient data; n, number; SE, standard error

Back to main deck: Key issue 6

Comparison of modelled health state utility values across different comparators and different sets of assumptions

EAG's comparison of modelled health state utility values

Table: Comparison of company and EAG modelled utility for an average 50-year-old patient just under 10-year post baseline, by treatment

	≥2 attacks for month			≥2 attacks for week		
Base case ⟶	**Company updated – annual attacks**	Company scenario – monthly attacks	**EAG updated – monthly attacks**	**Company updated – annual attacks**	Company scenario – monthly attacks	**EAG updated – monthly attacks**
Garadacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Berotralstat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lanadelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cinryze	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No prophylaxis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG: Using company's preferred assumptions would result in negative utility values for an untreated 50-year old patients with 2 or more attacks per week, which the EAG considers implausible

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

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

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

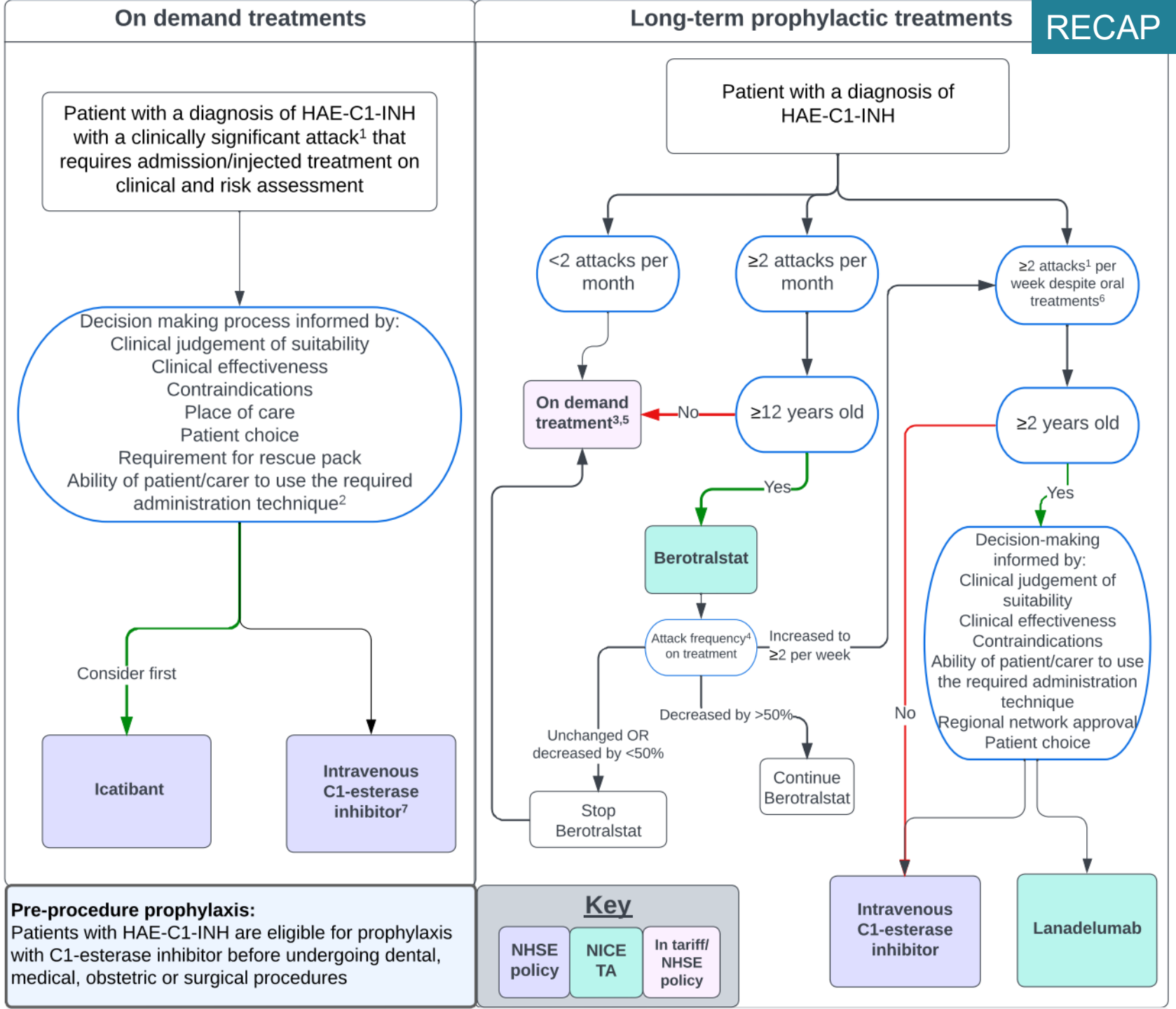
NICE

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

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



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 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

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	[redacted]	[redacted]
18 to <40 years	[redacted]	[redacted]
40 to <65 years	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]
Female, %	62	56
Mean weight*, kg (SD)	[redacted]	[redacted]
Bodyweight, %		
<50 kg	[redacted]	[redacted]
50 to <75 kg	[redacted]	[redacted]
75 to <100 kg	[redacted]	[redacted]
≥100 kg	[redacted]	[redacted]
Race, %		
White	85	88
Other	15	12

Table: HAE history of trial participants

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

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

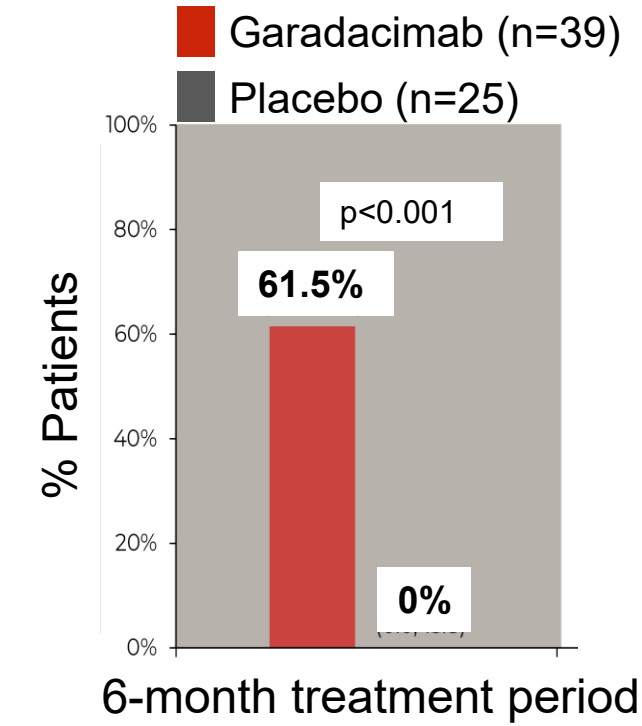
Clinical trial results

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

NICE

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

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])

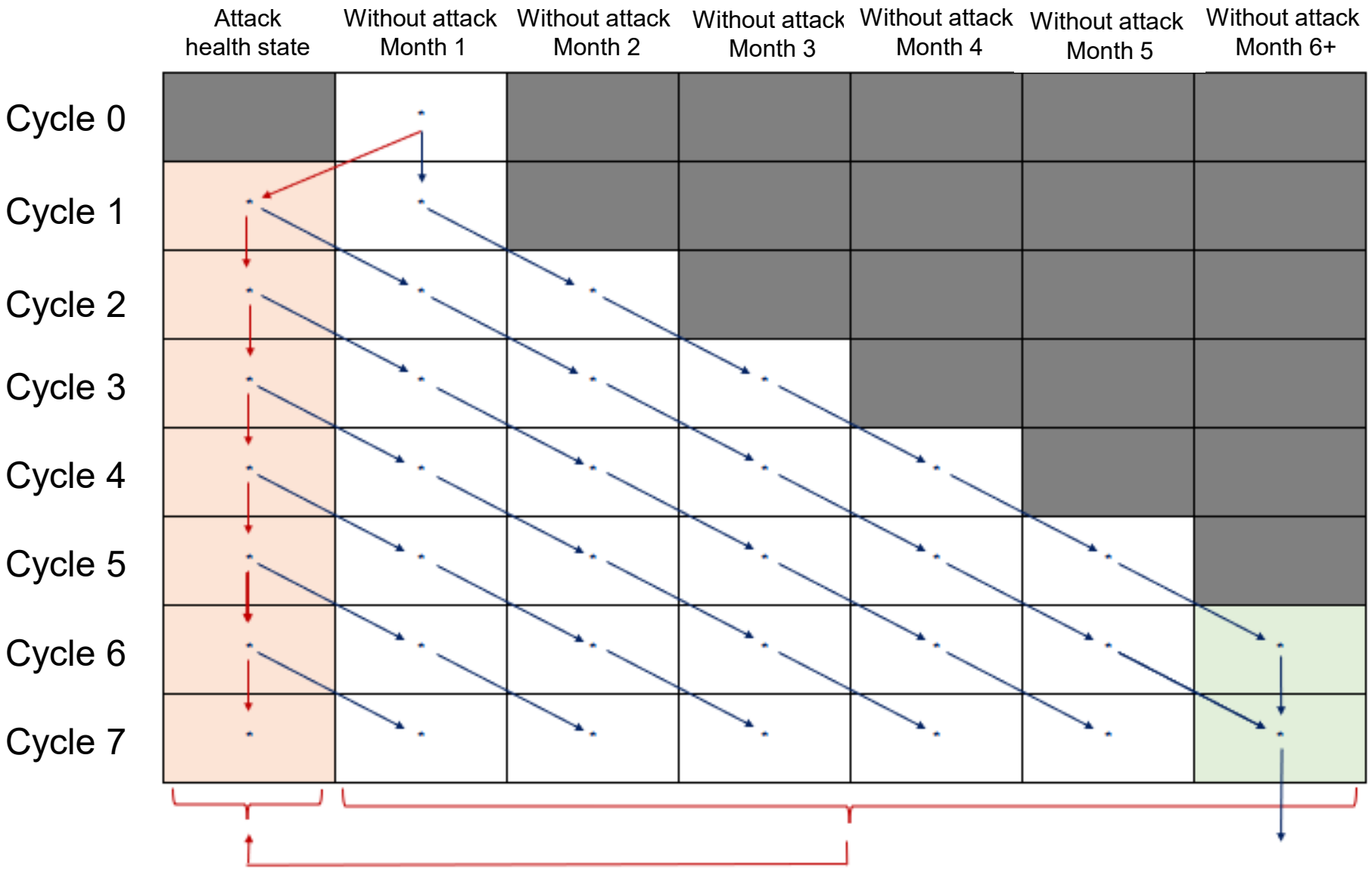
- Post-hoc analyses indicate efficacy of garadacimab in reducing time-normalised number of attacks from baseline is maintained beyond the randomised 6-month treatment period of VANGUARD with no evidence of waning of effect even after >2 years of treatment → mitigates uncertainty associated with relatively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

NICE

Abbreviations: CI, confidence interval; n, number

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

Company's model overview (1/2)



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)

RECAP

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) RECAP

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

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

Back to ACM2: Key issue 5

Approaches for lanadelumab switching between Q2W and Q4W

RECAP

Some differences in way company and EAG model lanadelumab dosing switch

Table: Comparison of company and EAG model assumptions after TE – recap of ACM1

Assumption	Company	EAG preferred
Proportion	45% switch to Q4W	45% switch to Q4W
Duration	6 months	6 months
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 • Those losing response would move back to Q2W dosing

NICE

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 (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

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

ACM1 summary of company / EAG modelling 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: Vignettes describing HAE context	Pennington et al 2024: SF-6D used in survey of UK household
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
Number of carers per household	1 (updated at TE stage)*	1
% of HAE attacks requiring carer 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

*NICE technical team would like to correct a factual inaccuracy in DG about carer number assumed by company – company updated this to 1 per household at TE so was aligned with EAG (= committee preferred)

NICE

Abbreviations: ACM1, 1st committee meeting; DG, draft guidance; HAE, hereditary angioedema; TE, technical engagement

Back to ACM2: Key issue 6

RECAP (corrected)

ACM1 calculation of patient utilities

Some differences in way company and EAG model patient utilities

Table: EAG's summary of approach implemented by company and EAG after TE – **recap of ACM1**

Feature	Company base case	EAG preferred approach
How HAE attack disutility calculated from Nordenfelt	Assumed 'attacks in past cycle' meant attacks in **past year**	Originally assumed 'attacks in past cycle' meant attacks in **past year**, but updated to in **past month** in model **post ACM1*** *Corrected
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

NICE

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

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: Key issues

RECAP

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?

Back to main deck: Key issues

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

RECAP

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

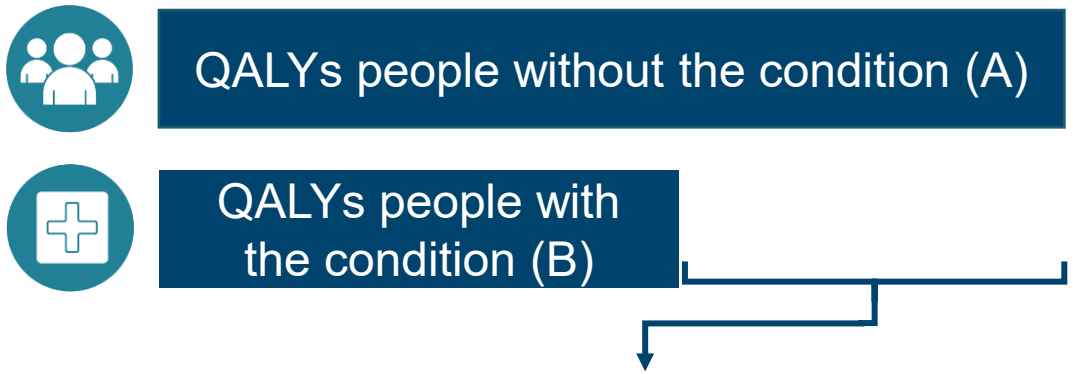
- Long-term effectiveness uncertain for all treatments. Garadacimab attack rates stable after first 6 months of treatment in OLE study (median [redacted] months treatment), but is a post-hoc analysis of small sample
- Company's original approach: did not fit data well as attack rates not constant in 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

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

Abbreviations: QALY, quality-adjusted life year

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**.